Glucophage® (Metformin Hydrochloride), the Wonder Drug: A Biguanide Class Treatment of Type 2 Diabetes

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Abstract

Diabetes is a disease that has been around for a very long time—from as far back as the ancient Egyptians. The disease does not have just one straightforward etiology, since there are several different types of diabetes. Type 2 diabetes affects at least 10 percent of the United States population, and one of the most recommended drugs in treating type 2 diabetes is metformin. Synthesized from a naturally occurring flower that had been used in the past to treat the symptoms of diabetes, metformin has many positive effects, including lowered hemoglobin A1c levels (HbA1c), weight reduction, and a lowered risk of heart attack. Metformin can also be used in treating other conditions, such as polycystic ovarian syndrome and cancer. Current research is even exploring metformin's ability to counteract aging. The exact mechanism of metformin is still being researched, but it is believed that the center of metformin's action is an alteration of the energy metabolism of the cell.

Introduction

Metformin is a member of the biguanide class of drugs and is used in treating a number of diseases and conditions, of which type 2 diabetes is most prevalent. Type 2 diabetes is characterized by abnormally high levels of glucose in the blood due to either insulin resistance of the cells or too much glucose production in the liver or a combination of both.

Metformin's mechanism of action is related to increasing the activity of energy sensor adenosine-monophosphate-activated protein kinases, which increases glucose uptake in various tissues, increases lipid metabolism, and decreases glucose production in the liver.[1,2,3] Thus metformin lowers blood glucose concentrations but also increasingly seems to produce a host of other beneficial effects in both diabetics and non-diabetics.

History and Epidemiology

Diabetes is an old disease, and can be found recorded as far back as 1500 BCE by Egyptian physicians.[4] Until the 1920s, when Banting and Best discovered how to extract and purify insulin, there was no efficacious treatment for diabetes.[5]

The different manifestations of diabetes include type 1 diabetes mellitus (T1D), type 2 diabetes (T2D), gestational diabetes mellitus, maturity-onset diabetes of the young, endocrinopathies, and diseases of the pancreas such as pancreatic cancer or pancreatitis. They all have differences in underlying pathogenesis, but the unifying theme is that when untreated they all result in chronic hyperglycemia.[6]

From 1980 to 2014, the rate of diabetes increased from 4.3% to 9.0% in men, and from 5.0% to 7.9% in women, to affect a total of 382 million people around the world.[7,8] In the United States, T2D affects 29.1 million people or 9.3% of the total population, according to the Centers for Disease Control and Prevention.[9] Factors contributing to this rising epidemic include aging, population growth, increasing urbanization, increasing incidence of obesity, and more inactive lifestyles.[7,10] However, T2D is only one classification of the many maladies that fall under the umbrella of diabetes.

T2D accounts for approximately 90% of all diabetic cases and is a condition in which the blood is hyperglycemic. Patients with T2D do not need insulin to survive but may present with varying severity of pathophysiologies ranging from predominantly insulin resistant with relative insulin deficiency to predominantly insulin secretory defect with some insulin resistance.[21] Setter and fellow researchers (2003) described T2D as "characterized by three pathophysiologic abnormalities: relative insulin deficiency, insulin resistance involving myocytes and adipocytes, and hepatic insulin resistance" which result in increased gluconeogenesis and impaired glycogen synthesis.[11] The risk of developing this form of diabetes increases with old age, obesity, and inactivity. It has ties with different ethnic groups and is also presumed to have a stronger association to genetics than the autoimmune form of diabetes, T1D.[4]

Untreated chronic hyperglycemia that results from T2D can result in severely detrimental side effects. These include nephropathy, neuropathy, retinopathy, and macrovascular complications. Of all deaths in patients with T2D, 80% involve cardiovascular disease or stroke, reflecting the macrovascular complications of the disease. Cardiovascular abnormalities can be a result of other factors, including obesity, lipid abnormalities, hypertension, hypercoagulation, platelet dysfunction, and endothelial dysfunction.[11] Neuropathy can potentially result in limb amputation; retinopathy can lead to blindness; and nephropathy leads to end-stage renal disease and the need for renal dialysis or transplants. Delaying or preventing these complications are primary goals in treating diabetes.[12]

In 1936 Harold Himsworth differentiated between insulin-sensitive and insulin-resistant types of diabetes.[13] This discovery opened the door for the array of T2D or insulin-resistant diabetic treatments. Drugs currently on the market for treating T2D include, but are not limited to, sulfonylureas, thiazolidinediones, biguanides, incretin mimetics, peroxisome proliferator-activated receptor gamma (PPARɣ), and α-glucosidase inhibitors.[14] The oldest of these drugs are the sulfonylureas, which were the primary treatment for T2D before metformin. The American Diabetes Association

(2014) recommends treating a patient with T2D by starting with lifestyle modifications such as diet and exercise.[12] Although these modifications are important, they are rarely completely efficacious in treating hyperglycemia. T2D is a progressively degenerative disease that worsens with age and involves progressive beta-cell functional decline. It is important to reassess patients every few months, whatever medication(s) they may be on.[15]

Sulfonylureas

Sulfonylureas were the primary treatment for T2D before metformin and now are sometimes used in combination with metformin.[6] Carbutamide was a first-generation member of the sulfonylurea family and was discovered in 1942 to be effective in treating hyperglycemia. However, carbutamide had adverse effects on bone marrow and so was withdrawn from the market.[14] In the 1960s, later generations of sulfonylureas were shown to be no more effective in treating T2D than diet and exercise, and thus were recommended as a first line of treatment in newly diagnosed patients.[16] Second-generation sulfonylureas with no adverse effects on the heart or bone are now on the market and possess effective mechanisms of lowering blood glucose concentrations.[14]

Sulfonylureas work as K^+ channel blockers and result in an increase of insulin secreted from the pancreatic β cells into the plasma, regardless of the concentration of blood glucose.[14] In addition to their effects on pancreatic β cells, sulfonylureas increase receptors for insulin on monocytes, adipocytes, and erythrocytes when the patient receives chronic treatment.[17] Depending on the generation, sulfonylureas are usually taken once a day with increasing dosages as needed and have an active duration of from 8-24 hours.[18]

The major limitation of sulfonylureas, especially with the longer-acting agents such as glyburide and chlorpropamide, is their high risk for hypoglycemia because they increase insulin secretion regardless of how much insulin is already in the blood.

Metformin

Metformin is in the class of biguanides and is currently a first-line treatment for T2D.[4,15,19,20] It is not insulin but is considered an insulin sensitizer.[21,22] It is in the biguanide family, isolated from the flower *Galega officinalis*, commonly known as goat's rue, and was used to treat diabetes in the medieval period because it relieved the intense urination.[5] In 1922 guanidine was found to be the active ingredient in *Galega officinalis* that lowered blood glucose levels.[23] Phenformin and buformin were synthesized as part of the biguanide class in the 1950s, but were withdrawn in the 1970s because of increased incidences of death due to lactic acidosis and cardiac dysfunctions resulting from use of phenformin in treating those with T2D.[23,24] Metformin was part of the next generation of biguanides, and in 1995, after 20 years on the market in the United Kingdom (UK), it was approved for use in the United States because it did not have the same toxic effects as phenformin.[5,23] The guanidine structure of metformin is a nitrogenous analog of carbonic acid, and includes two methyl groups, whereas phenformin and buformin have apparently toxic aromatic rings or alkyl chains. In Figure 1, the differences between phenformin and metformin can be observed.

Metformin has a greater association with reductions in weight and low-density lipoprotein (LDL) cholesterol, and a much lower risk of hypoglycemia when compared with sulfonylureas and with thiazolidinediones, a newer option in treating T2D.[20,26]

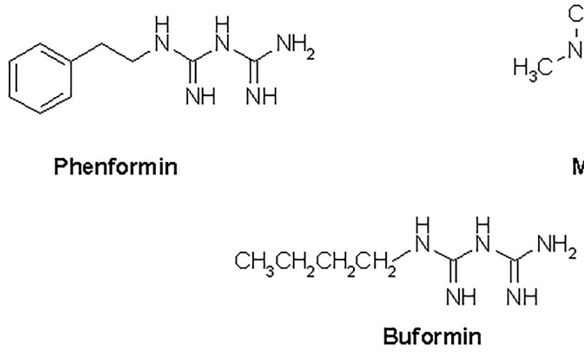

Figure 1. Differences in structure between phenformin, metformin, and buformin.[25]

Metformin carries a low risk of hypoglycemia because its primary action is inhibition of gluconeogenesis, the liver's production of glucose from non-carbohydrates such as proteins or fats. In contrast, the effect of most other T2D drugs is to stimulate insulin secretion. Metformin's beneficial effect on diabetes is dependent on there being circulating insulin in the blood.[27] Thus it cannot be a substitute for insulin or the only treatment in insulin-dependent diabetes such as T1D. Metformin is indicated in treating insulin-resistant classes of diabetes, such as T2D or gestational diabetes.

When compared against placebo effect or insulin, metformin also decreases cardiovascular mortality rates.[3,28] Along with these effects, metformin provides protection against nephropathy, heart disease, and polycystic ovarian syndrome, and a significant reduction in cancer risk.[3]

Development of Metformin

The botanical *Galega officinalis,* as previously mentioned, was given to diabetic patients because it relieved the excessive urination symptom. The plant is also known as French lilac or Italian fitch, and was given to patients during plague epidemics to promote perspiration.[5] Further research showed that the active ingredient in French lilac that resulted in lowering of blood glucose was galegine, or isoamylene guanidine.[28] Metformin is a substituted biguanide synthesized from the guanidine active principle and is shown in Figure 2a and Figure 2b. Metformin's official chemical name is N,N-dimethylimidodicarbonimidic diamide (also called 1,1-dimethylbiguanide), and its formula is C4H11N5.[29]

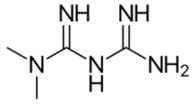

Figure 2a. Molecular structure of metformin.[29]

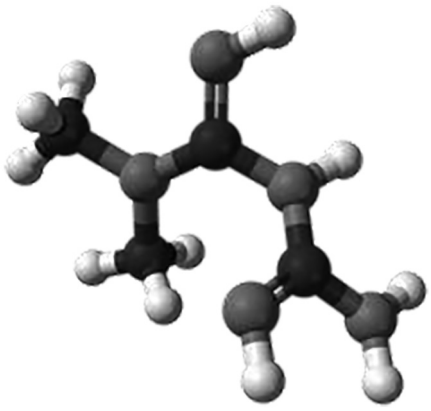

Figure 2b. Ball-and-stick model of metformin.[29]

Metformin was first described in 1922 by Werner and Bell, and it involved a simple precipitation reaction of dimethylamine hydrochloride and 2-cyanoguanidine over heat. This synthesis can be seen in Figure 3. More reactions to produce metformin have been described and patented. Metformin hydrochloride, the salt version of the drug, is synthesized via the reaction of equimolar amounts of dimethylamine and 2-cyanoguanidine dissolved in toluene with cooling to make a concentrated solution, with equimolar amounts of hydrogen chloride slowly added. The mixture boils and then, after cooling, metformin hydrochloride is yielded in a precipitate with 96% yield.[30,31]

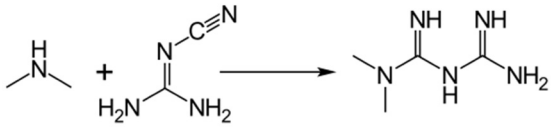

Figure 3. Synthesis of metformin first performed by Werner and Bell.[30]

In 1929 metformin was shown to lower blood glucose concentrations in rabbits and was the most efficacious out of all the biguanides studied simultaneously, but this discovery was overshadowed by the breakthrough of extracting and purifying insulin around the same time. Metformin was approved for the US pharmaceutical market in 1995, after recognition of the acidosis risk of phenformin, another member of the biguanide family.[32]

The dosage of metformin is usually 1-3 pills per day at different sizes of 500 mg, 850 mg, or 1000 mg, taken with meals in order to reduce adverse gastrointestinal side effects.[22] The dosage is usually changed when taken in combination with other drugs. Metformin can be used concomitantly with other drugs such as glipizide, glyburide, rosiglitazone, pioglitazone, repaglinide, sitagliptin, and insulin to create beneficial glucose-lowering effects.[33]

Testing and Clinical Trials

Organic Cation Transporter

Shu and colleagues (2007) performed testing on hepatic tissues *in vitro* and in mice *in vivo*, showing that the organic cation transporter-1 (OCT1) is important in metformin activity.[1] The researchers determined that, in primary cultures of mouse hepatocytes, elimination of *Oct1* gene reduced the response to metformin. And *in vivo* testing in mice showed that OCT1 was required for metformin to lower blood glucose levels. They also observed in humans that OCT1 polymorphisms modulated cellular and clinical responses to metformin, and concluded that OCT1 mediates the first step in the response pathway of metformin.[1] Thus, changes in *Oct1* expression, or prevalence, may change the effectiveness of metformin in humans.[3]

Type 2 Diabetes

Various clinical trials have shown that metformin has many more positive effects than simply lowering HbA1c levels, which it was originally used to do. Metformin has also been shown to decrease cholesterol levels, reduce weight, and prevent death due to cardiovascular disease (CVD).[22]

Metformin's glucose-lowering capability is related to its ability to perform a long list of functions. Metformin improves glucose metabolism and insulin action by having a positive effect on insulin receptor expression as well as tyrosine-kinase activity.[2,3] Metformin's binding interactions result in increased adenosine monophosphate (AMP)-activated protein kinase (AMPK) activity, which increases adenosine triphosphate (ATP)-generating pathways and decreases the ATP-consuming pathways. AMP and ATP are involved in regulating certain biochemical cellular processes, such as lipid metabolism, membrane transport and cell proliferation. The binding interactions increase mitochondrial biogenesis and lipid oxidation, as well as insulin sensitivity.[31]

AMPK is activated by metformin's binding to the respiratory chain complex.[34,35] El-Mir, Nogueira, and Fontaine (2000) discovered "the treatment by dimethylbiguanide *in vivo* or *in vitro* (in intact isolated hepatocytes) affects the mitochondrial respiratory chain specifically at the complex I site," and isolation of the other protein complexes in the respiratory chain did not prove effective. They also concluded, by testing *in vitro* hepatocytes, that reactive oxygen species (ROS) scavengers had no effect on metformin nor on its action.[35]

Testing also showed that metformin increases plasma levels of glucagon-like peptide 1 (GLP1), which helps with insulin signaling.[36] GLP1 is secreted from the gut in response to ingestion of food. In people not suffering from diabetes, GLP1 stimulates insulin secretion, while in T2D patients GLP1 activity is not efficient or it is suppressed.[37]

Howlett and Bailey (1996) assert that metformin has been shown not only to lower blood glucose concentrations, but also to positively impact lipids and triglyceride levels in the blood in patients with T2D. It can produce a 10 to 20 percent reduction in plasma triglyceride levels in non-hypertriglyceridemic patients and up to 50 percent triglyceride reduction in hypertriglyceridemic patients, a 10 percent decrease in total cholesterol levels, an increase of 17 percent in high-density lipoprotein (HDL) levels, and a 25 percent decrease in low-density lipoprotein (LDL) levels.[38]

Metformin is beneficial in reducing cholesterol not only in diabetic patients but non-diabetics as well. Carlsen and colleagues (1996) noticed a 12 percent decrease in lipid levels over a 12-week period and reported that "metformin, given for 12 weeks as a supplement to lovastatin, diet and lifestyle advice to non-diabetic male patients with coronary heart disease, further improves the lipid pattern in normal weight patients, and reduces weight in the overweight patients."[39]

ILamanna and fellow researchers (2011) concluded that, in reducing CVD risk, metformin was more beneficial in its effects on cardiovascular events in trials that had longer lengths with younger participants, and that the greatest benefit of metformin in reducing CVD and all-cause mortality derives from its glucose- and lipid-decreasing factors.[40] According to Bristol-Myers Squibb, the company that markets Glucophage, other studies have shown more concrete evidence that metformin significantly decreases CVD mortality risk.[35]

According to Rafieian-Kopaei and Baradaran (2013), metformin may have renoprotective qualities as well.[40] Glycosuria, a condition characterized by high levels of glucose in the urine is harmful to the renal tubules because it can disrupt the filtering capabilities of the glomeruli and lead to kidney damage. Metformin decreases incidences of glycosuria and also possesses antioxidant effects, which contribute to less damage in the kidneys.[41]

As of 2012, metformin is not indicated as a weight-loss drug, even though studies have shown that metformin reduces weight and can prevent the development of T2D.[42,43] The Diabetes Prevention Program Research Group (2012) administered a study on approximately 3,200 participants who were classified as pre-diabetic, which means that they had impaired glucose tolerance of 140-199 mg/dL and impaired fasting glucose of 95-125 mg/dL. The participants also had to meet certain BMI and age criteria. The researchers randomly separated participants into two groups, one receiving metformin and the other a placebo. Those in the metformin group saw a 3.5 percent weight reduction and lost at least 2 cm from their waist circumference over a period of 2 years.[42]

Type 1 Diabetes

According to Lund and colleagues (2009), patients with T1D that have poor glycemic control have just as much risk for cardiovascular disease and dyslipidemia, thus they benefit equally from metformin therapy. In a randomized controlled study of one-year length, 100 subjects with T1D and poor glycemic control were given adjunct metformin therapy in combination with insulin or other drugs. Overall, the subjects involved in the study had a decrease of 0.3 mmol/L in both total and LDL cholesterol. The results in HDL cholesterol were not significant, however.[44]

Other studies show similar results. Abdelghaffar and Attia (2009) observe that "studies done in type 1 diabetes demonstrated different combinations of the following: reduction of glycosylated hemoglobin A1c, increased insulin sensitivity, decreased dosage of insulin, decreased body mass index, and improvement of lipid profile." [45] The safety of metformin in T1D may be questionable because the drug comes with a higher risk for lactic acidosis and hypoglycemia than when used as treatment in patients with T2D. The main effect of metformin in T1D is most likely due to its insulin-sensitizing effect, in contrast to metformin's effect in T2D in contributing to decreased hepatic glucose output.[46]

Contraindications and Side Effects

The main concerns with any available treatment for diabetes include hypoglycemia and diabetic ketoacidosis. Diabetic ketoacidosis (DKA) as a result of prolonged elevation of glucose in the blood is a very serious state. It includes severe dehydration from a combination of loss of electrolytes, sweating, hyperventilation, and fever, as well as includes cardiac and skeletal muscle toxicity.[47] DKA can be easily avoided with close monitoring of blood glucose levels. One out of 33,000 patients taking Glucophage reports incidences of DKA in a year.[22] According to Cusi and Defronzo (1998), "Unlike phenformin (a precursor to metformin of the biguanide family), metformin does not adversely affect mitochondrial lactate oxidation and therefore does not cause lactic acidosis unless plasma concentrations of metformin are excessive."[24]

Adverse Reaction	GLUCOPHAGE Monotherapy (n = 141)	Placebo (n=145)
Diarrhea¶	53.2	11.7
Nausea/Vomiting	25.5	8.3
Flatulence	12.1	5.5
Asthenia	9.2	5.5
Indigestion	7.1	4.1
Abdominal Discomfort	6.4	4.8
Headache	5.7	4.8

Table 1. Most common adverse reactions (>5.0 percent) in a placebo-controlled clinical study. Numbers listed as percentages of patients that experienced symptoms.[22] (Diarrhea led to a discontinuation of the study in 6% of patients receiving the Glucophage monotherapy.)

Metformin does not cause hypoglycemia by itself, but when used in combination with other diabetic treatments, there is potential for hypoglycemia.[24] Hypoglycemia can be avoided by careful monitoring of blood glucose levels.

Gastrointestinal effects occur in up to 50% of patients using metformin. They include bloating, diarrhea, nausea, abdominal pain, flatulence, anorexia, and dyspepsia, but these symptoms are almost always transient and resolve within a few days, especially when metformin is taken with food or in a gradual titration.[6,22] Common side effects can be seen in Table 1.

The major route of elimination of metformin is via the renal tubules, so any known compromised kidney function is a contraindication for the drug because it increases the risk of DKA. Metformin is also contraindicated in hypoxic conditions such as cardiovascular collapse, acute myocardial infarction, congestive heart failure that requires pharmacological treatment, and acute or chronic metabolic acidosis.[11] However, recent research has shown the positive effects of metformin on cardiovascular events, leading to an indication that it may be beneficial to use in patients with cardiovascular disease histories and may even help prevent cardiovascular events.[3,22] Lastly, metformin is contraindicated in patients with severe liver dysfunction and severe chronic obstructive pulmonary disease because these disorders increase the acidic state of the patient, which could potentially lead to DKA.[11]

Mechanism of Action

For a long time, metformin's mechanism of action (MOA) was unknown.[4,6,27] Since the drug was first synthesized in 1922, it has taken almost 80 years to start comprehending the cellular and molecular mechanisms. Even though much more is now known about the multiple effects of metformin, the mechanisms of these pleiotropic effects are still ambiguous.

It is believed that, in counteracting hyperglycemia, metformin binds to the protein complex 1 in the respiratory complex chain. In Figure 5 this binding is visualized. To get to the protein complex 1 in the mitochondrial membrane, metformin must first be transported inside the cell via organic cation transporter 1 (OCT1).[1,3] Metformin has a pKa of 12.4, so it is fully protonated and positively charged at physiologic pH; thus it does not passively diffuse through the cell.[3] That is why OCT1 is so important in metformin's action, and deletion of the *Oct1* gene can cause metformin to be ineffective.

When metformin binds to protein complex 1 in the mitochondrial membrane it causes inhibition of the electron transport chain, which leads to decreased levels of cyclic adenosine monophosphate (cAMP) in the cell, which leads to decreased ATP production. This activates adenosine monophosphate kinase (AMPK), which leads to an increased activity in the ATP-generating pathways and decreased activity in ATP-consuming pathways to counteract the imbalance.[3] By increasing and decreasing these pathways, metformin helps the patient regulate homeostatic levels, keeping circulating lipids, glucose, and insulin levels low. AMPK decreases glucose levels, ectopic fat deposition, insulin secretion, glucose production, lipid synthesis, lipolysis, and lipogenesis. Increased AMPK activity increases glucose uptake, lipid oxidation, mitochondrial biogenesis, and insulin sensitivity.[31] The systemic effects of AMPK activation listed can be seen in Figure 6.

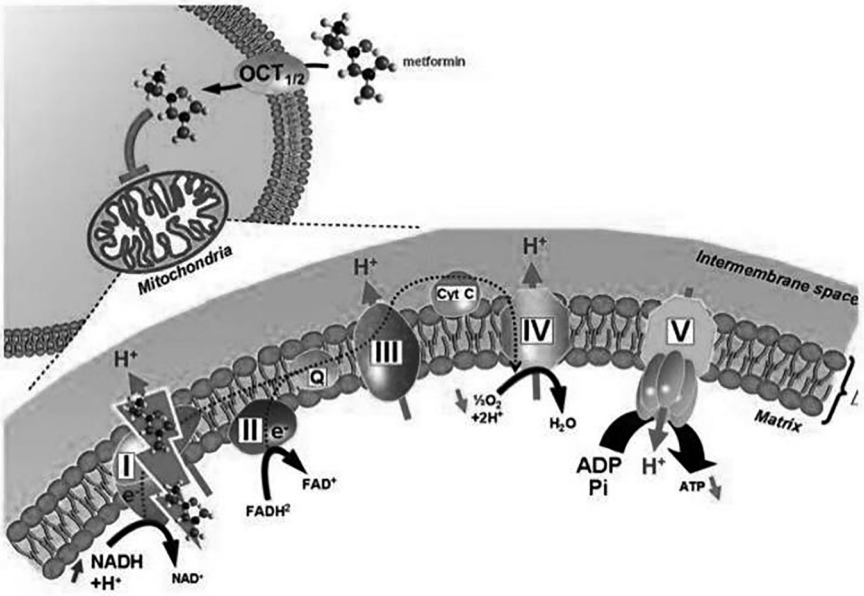

Figure 5. Metformin's mechanism of action in the respiratory chain complex.[3]

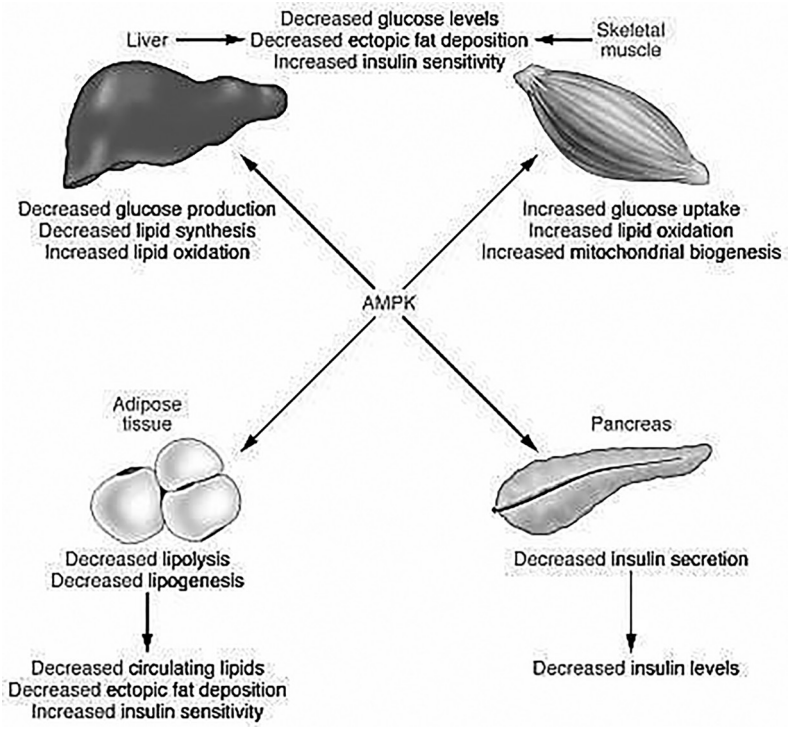

Figure 6. Systemic effects of metformin.[31]

Polycystic ovarian syndrome (PCOS) affects approximately 10 percent of women; it is an endocrinopathic condition in which cysts develop on the ovaries, leading to increased androgen production, insulin resistance, amenorrhea, and anovulation.[48] When administered to women with PCOS, metformin has been shown to increase ovulation, improve menstrual regularity, reduce serum androgen levels, and improve insulin sensitivity.[49] The exact molecular mechanisms of metformin in these effects remain elusive, but it is thought that they are a result of decreased insulin exposure in the ovaries.[3] High levels of insulin in the ovary have been shown to increase activity of steroidogenic enzymes.[50]

In clinical trials metformin has also been shown to reduce risk of abortion in women with PCOS, by increasing factors such as IGFBP-1 and glycodelin levels, as well as increasing uterine blood flow, which protect the developing embryo and fetus. Metformin also decreases factors such as endometrial androgen receptor expression, PAI-1, and plasmic ET-1, which at high levels increase risk for abortion.[3,50] Again, the mechanisms that cause these effects are unknown, but the effects may be in part due to metformin's improvement of insulin sensitivity.[3]

Heart disease is a major threat to patients with T2D; in fact, it is the leading cause of death in those with T2D.[9,51] But metformin can reduce diabetes-related death and all-cause mortality by 42 and 36 percent, respectively, as demonstrated in the longitudinal UK Prospective Diabetes Study (UKPDS), which followed approximately 1700 T2D patients for 10 years and was reported in 1998.[52] The lower death rates among those administered metformin can be attributed to the AMPK activation and reduced amounts of ATP.

Forouzandeh and fellow researchers (2014) discovered the benefits of metformin in combating heart disease in mice and concluded that

> metformin attenuates atherosclerosis and vascular senescence in mice fed a high-fat diet and prevents the upregulation of angiotensin II type 1 receptor by a high-fat diet in the aortas of mice. Thus, considering the known deleterious effects of angiotensin II mediated by angiotensin II type 1 receptor, the vascular benefits of metformin may be mediated, at least in part, by angiotensin II type 1 receptor downregulation.[43]

Pharmacokinetics

According to Bristol-Myers Squibb Company, Glucophage (metformin) has an absolute bioavailability under fasting conditions of 50 to 60 percent. Since metformin is usually taken with food, absorption is decreased and slightly delayed in regular usage, but the clinical relevance of metformin's potency decreasing with food is unknown. Maximum levels of concentration are achieved within a median value of 7 hours and a range of 4 to 8 hours. Interestingly, high-fat or low-fat meals made no differences in the maximum concentration of Glucophage.[22]

Whereas sulfonuylureas are 90% bound to plasma proteins, metformin is negligibly bound and partitions into erythrocytes as a function of time. The apparent volume of distribution averaged 654 ± 358 L in clinical trials. Steady state plasma concentrations are reached in 1 to 2 days.[22]

Metformin is excreted unchanged in renal tubules and does not undergo hepatic metabolism or biliary excretion, as evidenced by the renal clearance of metformin being 3.5 times greater than creatinine clearance. After 24 hours, approximately 90 percent of metformin is eliminated via the renal tubules.[22]

Future Directions

Metformin has been shown to reduce inflammatory markers in obese mice fed a high-fat diet. Kim's team (2013) discovered that several markers—including TNF-alpha, IL-6, leptin, resistin, tPAI-1, and MCP-1—were all significantly reduced in the obese mice when administered metformin, compared to control groups.[53] Since inflammatory markers are a part of the metabolic syndrome and are related to developing obesity, T2D, and cancer, more research is currently delving into utilizing metformin as an anti-cancer agent. Metformin's anti-cancer effect may be related to its antioxidant capabilities.[54]

Onken and Driscoll (2010) discovered that metformin increased the lifespan of aging *Caenorhabditis elegans*, a dirt worm, by inducing a dietary restriction-like state:

> We report that metformin extends *C. elegans* median lifespan via a mechanism that requires the cellular energy sensor AMPK, its upstream activating kinase LKB1, and the downstream DR/oxidative stress responsive transcription factor SKN-1, but is independent of the insulin signaling pathway components that modulate longevity. Our data on metformin outcomes are consistent with the interpretation that metformin acts, at least in part, as a dietary restriction mimetic in *C. elegans* and suggest that this activity is executed via a mechanism that is conserved from nematodes to humans. Implications of these findings could influence development of plausible anti-aging therapies based on a drug currently used in the clinic. [55]

Martin-Montalvo and fellow researchers (2013) found metformin to increase the lifespan in mice by mimicking the bodily effects of calorie restriction, even though food intake was increased.[56] They suggest that an adaptation to metformin occurs, leading to reduced oxidative stress and increased antioxidant defenses, which contribute to lower oxidative damage accumulation and inhibition of chronic inflammation.[56]

The UKPDS longitudinal study not only found a reduction in mortality due to heart disease, as stated earlier, but also found that metformin increases the longevity of life in high-risk diabetic patients as compared to sulfonylureas.[52] To assess its anti-aging properties, metformin is currently being administered in a 6-year-long clinical trial, labeled the Targeting Aging with Metformin (TAME) study, with 3000 elderly people who meet certain high-risk characteristics.[57] Various websites and magazines have latched onto this study, and they tout the claim that metformin could increase the average expected lifespan to 120 years.[57,58,59]

Developing Drugs

New drugs on the market to treat T2D include thiazolidinediones (TZDs), peroxisome proliferator-activated receptor gamma (PPARɣ)[2], meglitinides, and milk protein-based enzymes.

TZDs promote fatty acid uptake and storage in adipose tissue, according to the "fatty acid steal" hypothesis. They "increase adipose-tissue mass and spare other insulin-sensitive tissues such as skeletal muscle and the liver, and possibly pancreatic beta cells, from the harmful metabolic effects of high concentrations of free fatty acids. Thiazolidinediones thus keep fat where it belongs."[60] With TZDs, adipose tissue expression and serum concentrations of adiponectin also increase. This effect, combined with the lowering of serum free fatty acid levels, contributes to increased hepatic insulin sensitivity, the lowering of hepatic fat content, and the inhibition of hepatic glucose production. Thus glucose concentrations in the blood decrease and serum insulin concentrations decrease as a consequence of enhanced insulin sensitivity and clearance.[60] The most serious contraindication of TZDs applies to patients with heart failure, because of the potential to cause heart failure due to salt/fluid retention.[15] Also, first-generation TZDs caused serious liver damage in patients, but the newer generations are not as apt to cause such harm.

Meglitinides are similar to sulfonylureas in that they block potassium channels in the beta cell, but they also have the same hypoglycemic effects as sulfonylureas.[19] The meglitinides have a rapid response in insulin secretion and a short half-life.[61]

The newest drugs, still being researched, are protein- and hormone-based enzymes, alpha-glucosidase inhibitors and dipeptidyl peptidase-IV (DPP-4). These are milk-protein-derived peptides found in fermented dairy or other foods containing bioactive peptides that may have positive impacts on bodily functions or conditions, and ultimately benefit overall health. They are currently the subject of intensive research.[7]

Alpha-glucosidase inhibitors inhibit the enzyme alpha-glucosidase, which digests carbohydrates, at the enteric brush-border.[19] Use of these inhibitors results in an increase in overall carbohydrate digestion time, and less glucose is absorbed.[62,63] DPP-4 is a multifunctional transmembrane protein that is widely distributed in different organs and tissues, including the exocrine pancreas, sweat glands, salivary glands, mammary glands, thymus, lymph nodes, intestines, biliary tract, kidney, liver, placenta, uterus, prostate, brain, blood cells, and integument. It is known for inactivating the incretin hormones GLP-1 and GIP via cleavage of peptide bonds after proline or alanine. Since GLP-1 and GIP are hormones that are released after eating and enhance up to 60% of the postprandial insulin release, inhibition of the DPP-4 enzyme allows GLP-1 and GIP to continue enhancing insulin release.[7]

The current evidence shows that alpha-glucosidases and DPP-4 can be found in whey protein isolates and, when administered in conjunction with a meal, T2D patients experienced improved insulin release. When administered in isolation, milk-derived peptides have been shown to have detrimental side effects.[7] Researchers note that, as a consequence,

> there is an increasing attention toward natural, safe, food-derived peptide inhibitors as these are without any side effects. Milk protein-derived peptides with alpha-glucosidase and DPP-IV inhibitory traits potentially regulate the postprandial hyperglycemia in healthy and T2D subjects by inhibiting both the inactivation of the incretin hormones and the carbohydrate hydrolyzing enzymes.[7]

Conclusions

Despite the wide array of options for treating T2D, metformin remains one of the best anti-diabetic drugs on the market because of its efficiency in lowering blood glucose levels in patients with T2D and its extremely low risk of side effects such as hypoglycemia and acidosis. Instead of compounding the issue by simply adding more insulin or stimulating more insulin secretion as other common diabetic agents do, metformin works with the body to regulate homeopathic processes. It is currently indicated to treat not only insulin-resistant diabetes such as T2D and gestational diabetes, but also polycystic ovary syndrome. The full pleiotropic effects of metformin may not yet be fully discovered, and it is currently being researched for anti-cancer and anti-aging treatments. Lastly, metformin is an affordable option due its simple synthesis and cost effectiveness.

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