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A Review on Metformin

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ABSTRACT :

An antihyperglycemic medication called metformin (dimethylbiguanide) is used to treat diabetes mellitus that is not insulin-dependent. It counteracts insulin resistance by increasing glucose consumption and decreasing glucose synthesis when insulin is present. Metformin side effects include decreased hepatic gluconeogenesis, increased intestinal glucose absorption, increased muscle glucose uptake, oxidation, and glycogenesis, and maybe a decreased rate of intestinal glucose absorption. Numerous studies have suggested that adenosine monophosphate (AMP)-activated protein kinase (AMPK), the cell's fuel gauge, may have a direct or indirect role. There is evidence that metformin may have a mildly inhibitory effect on mitochondrial complex 1, which would raise AMP and activate AMPK. In this review, we assess the data critically.

Metformin hydrochloride, Anti-hyperglycemic, Adenosine mono phosphate(AMP), Adenosine mono phosphate-activated protein kinase (AMPK), Glycogenesis, Diabetes mellitus.

Introduction:

The synthesis of galegine-like chemicals from Gallega officinalis, a plant that has been used for centuries in Europe as a medication to treat diabetes, marked the beginning of the metformin discovery.They noticed that metformin's ability to lower blood sugar was correlated with its dose-response, and that there was a large safety margin when it came to metformin toxicity.In most nations, the most widely used oral glucose-lowering drug is metformin hydrochloride, a biguanide that is commonly referred to as "foundation therapy" for those with recently diagnosed type 2 diabetes mellitus.They noticed that metformin's ability to lower blood sugar was correlated with its dose-response, and that there was a large safety margin when it came to metformin toxicity.The most widely used oral glucose-lowering drug in most nations is the biguanide metformin hydrochloride, which is commonly known as "foundation therapy" for people with recently diagnosed type.

First-line anti-hyperglycemic treatment for type 2 diabetes mellitus (T2DM) is metformin, an insulin-sensitizing synthetic biguanide that is taken orally (1). For most patients, it is the only medication of its kind. The creation of metformin began in 1922, when folk medicine revealed that the French lilac, Galega officinalis, had the guanidine galegine, which was an active but toxic ingredient that might be used to treat "sweet urine" (2, 3). Metformin was first prescribed for type 2 diabetes in France in 1958, and more than 150 million people worldwide currently take it every day (4). Given that it is no longer under patent, metformin is generally safe and has the least amount of adverse effects. It is also a very cheap medication.

The WHO estimates that heart disease and diabetes account for about 22 million deaths worldwide each year (22). The fact that metformin is used so extensively presents an opportunity to ascertain whether or not it actually possesses anti-aging qualities. This objective begs the question, "What exactly constitutes an anti-aging drug?" The term "anti-aging action" refers to the prevention and treatment of age-related disorders; in other words, it is an activity that "positively affects healthspan," which is defined as "the period of life spent in good health and free of disabling diseases." Although there is widespread usage of the word "healthspan," we recognize that some people find it contentious because it is subjective and difficult to quantify. As a result, we continue to use it consistently, acknowledging its limitations and the fact that it only refers to a decrease in the chance of a crippling illness. Even yet, the decrease might lengthen life (23). Thus, extending life expectancy, or lifespan (longevity), which is defined as "the length of time an organism lives, or total lifespan," is not the same as prolonging healthspan. Longevity may be easily measured.

Literature review:

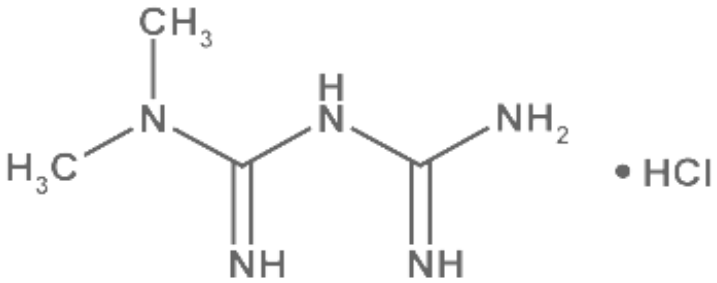
K Sreekumaran Nair, M.D., Ph.D., at the Mayo Clinic in Rochester, who specializes in endocrinology, diabetes, metabolism, and nutrition, states: "Many new oral therapeutic agents are emerging in response to the rapidly rising prevalence of T2DM, but metformin still dominates, both as monotherapy and in combination with other medications, including insulin. Metformin is a safe treatment for pregnant women with gestational diabetes and can help prevent or delay the formation of type 2 diabetes in sensitive groups, such as those with prediabetes, poor glucose tolerance, or fasting hyperglycemia.

Haleigh A. James, M.D "One of its major advantages is that metformin does not cause significant hypoglycemia," says Haleigh A. James, M.D., an endocrine trainee at the Mayo Clinic campus in Minnesota who specializes in endocrinology, diabetes, metabolism, and nutrition. Metformin treatment has an additional benefit in that it does not result in weight gain, unlike hypoglycemic medications like insulin or sulfonylureas, albeit it may induce slight weight reduction. According to some findings, metformin may have somewhat anorexic effects due to its hypothalamus effects and is linked to preferred fat loss. Metformin may lower the risk of cardiovascular events, despite inconsistent data, particularly in overweight T2DM patients. Metformin's mild effects on lowering blood pressure (which are unrelated to weight reduction), enhancing endothelial function and lipid profiles (particularly triglycerides), decreasing fibrinogen levels, and potentially boosting fibrinolysis may contribute to this positive effect.

According to **Dr. Nair**, these symptoms can be lessened by taking metformin with a sustained-release formulation or in the middle of a meal. They are more likely to happen when patients take the medication on an empty stomach. Although the precise causes of the gastrointestinal side effects are unknown, there is evidence that metformin may boost the gut's local production of serotonin. Metformin taken with a meal may have a comparable impact to slow-release metformin, which does not raise blood metformin levels quickly.

Pharmacological class:

Metformin is in a class of drugs called **biguanides**. Metformin helps to control the amount of glucose (sugar) in your blood.



Molecular formula: *C4H12ClN5*

Molecular weight: *165.62g/mol*

Brand names:

- Glumetza
- Formatat
- Glucophage
- Metatime-500

Iupac name: N,N-Dimethylimidodicarbonimidic diamide

Physical properties of metformin:

- ✓ **Nature:** White, hygroscopic crystalline powder
- ✓ **Solubility:** Freely soluble in water

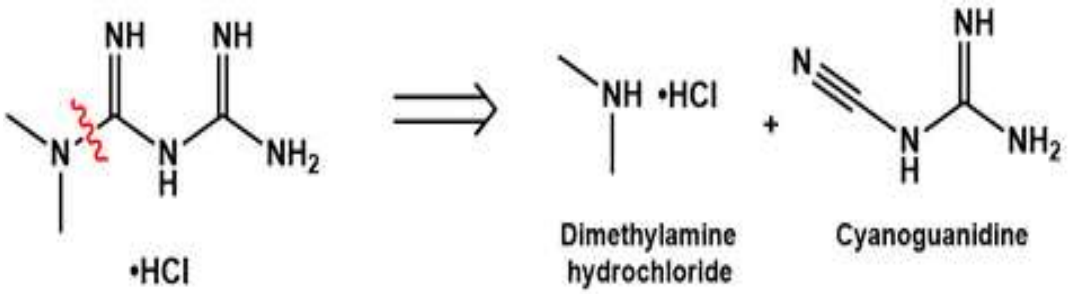
Slightly soluble in ethanol

Insoluble in acetone, ether or chloroform

- ✓ **Melting point:** 222-226^{0}C
- ✓ **Dissociation Constant(pKa):** 12.4

Synthesis of the metformin:

- The procedure consists of starting with 40% dimethylamine as a starting material, salinizing it using hydrochloric acid, and then exposing the resulting salt to the dimethylamine hydrochloride.
- Dicyclandiamide is added to an addition process in solvent N, N-dimethylformamide, to produce a crude product of metformin hydrochloride. Refinement is then carried out to yield metformin hydrochloride.



- A standard experiment involved performing a test reaction on a 5 x 20 cm TLC plate, placing a spot of solution containing 0.42 g of dicyanodiamide and 0.4 g of dimethylamine hydrochloride in 5 ml of ethanol on the plate, and then subjecting it to MWI at 540 W for 5 minutes, with intervals of 40 seconds.
- The TLC plate was then operated in the proper system. Metformin hydrochloride was observed in a noticeable patch, the rf value of which matched that of the reference sample. The reaction was run on a preparative TLC plate in order to obtain a sizable yield of pure product.
- On a preparative TLC plate, a range of reactant spots for the synthesis of metformin hydrochloride were placed beside a reference TLC plate containing two spots (one representing the reactant and the other representing the predicted result).
- For five minutes, MWI was applied to both plates sporadically at 40-second intervals at 540 watts.
- After viewing the reference TLC in an iodine chamber, the product-containing silica gel section was scraped off the preparative TLC plate, and the product was extracted using ethyl alcohol. The intended product yielded 0.82 g (92% yields) upon solvent evaporation.

Mechanism of action:

Many possible mechanisms of action have been suggested, including complex IV-mediated inhibition of the GPD2 variant of mitochondrial glycerol-3-phosphatedehydrogenase (thus reducing glycerol-derived hepatic gluconeogenesis), inhibition of the mitochondrial respiratory chain (complex I), activation of AMP-activated protein kinase (AMPK), inhibition of glucagon-induced elevation of cyclic adenosine monophosphate (cAMP) with reduced activation of protein kinase A (PKA), and an impact on gut microbiota. In most cases, metformin also has anorexiant effects, causing a reduction in calorie intake.

Metformin reduces the liver's process of gluconeogenesis, or the generation of glucose. Metformin's insulin-sensitizing effect is partially explained by its inhibition of growth hormone, adrenocorticotropic hormone, follicle stimulating hormone, and proopiomelanocortin expression from the pituitary gland. Metformin also has multiple actions on tissues such as the liver, skeletal muscle, endothelium, adipose tissue, and the ovaries.Metformin treatment lowers gluconeogenesis by more than one-third in patients with type 2 diabetes, who typically have three times the usual rate of this process.

Pharmacokinetics:

- Metformin is absorbed slowly and has a 50–60% oral bioavailability while fasting.
- After ingesting immediate-release metformin, peak plasma concentrations (Cmax) are reached in 1-3 hours, and with extended-release formulations, it takes 7-8 hours.
- There is no metabolism of metformin. Within 24 hours of a single oral dosage, it is eliminated from the body by tubular secretion and eliminated unaltered in the urine. It is also undetectable in blood plasma.
- Plasma has an elimination-half life of 6.2 hours on average. Red blood cells are where metformin is transported and appears to accumulate. Its elimination half-life is significantly longer—17.6 hours.

Pharmacodynamics:

- One significant hormone that controls blood sugar levels is insulin. Decreased sensitivity to insulin causes blood glucose levels to rise when the pancreas is unable to make up for it, which is the hallmark of type II diabetes.
- Type 2 diabetes patients may also have insulin insufficiency, which occurs when insulin cannot affect tissues and cells in a way that is sufficient (insulin resistance).

- Through an increase in peripheral glucose uptake and utilization, metformin lowers intestinal glucose absorption, lowers hepatic glucose synthesis, and improves insulin sensitivity. When using metformin, insulin secretion remains constant, in contrast to medications of the sulfonylurea class that cause hyperinsulinemia.
- Impact on glycosylated haemoglobin (HbA1c) and fasting plasma glucose (FPG) HbA1c is a crucial glycemic control periodic measurement that is used to track diabetes patients. An further helpful and significant indicator of glycemic management is fasting plasma glucose.
- Metformin reduced fasting plasma glucose levels by an average of 59 mg/dL from baseline in a 29-week clinical trial of participants with type II diabetes, while placebo subjects experienced an average increase of 6.3 mg/dL from baseline.
- HbA1c, or glycosylated haemoglobin, rose by 0.4% in individuals receiving a placebo alone and fell by around 1.4% in those receiving metformin.

Metformin hydrochloride can be formulated as:

Metformin immediate-release formulations:

When treating type 2 diabetes in adults and children patients ≥10 years old, metformin is recommended as an addition to diet and exercise to enhance glycemic control.

Metformin extended-releasetablet(XR):

For individuals with type 2 diabetes mellitus, the extended-release version of metformin is recommended as a supplement to diet and exercise in order to enhance glycemic control. Children's safety has not yet been established.

Metformin combination products:

Combination medicines containing metformin and additional anti-diabetic medications are available. It is recommended in adult patients with type 2 diabetes mellitus in conjunction with diet and exercise to improve glycemic control. In addition, it can be used in conjunction with SGLT2 inhibitors (canagliflozin, empagliflozin, erutgliflozin, or dapagliflozin), DPP-4 inhibitors (Sitagliptin, Linagliptin, alogliptin, or saxagliptin), or pioglitazone.

Metformin uses:

- Metformin mainly used to treat hyperglycemia caused by a type of diabetes mellitus
- Other uses of metformin:

Its being used off-label to treat:

- ✓ Weight reduction
- ✓ Polycystic ovarian syndrome(PCOS)
- ✓ Infertility
- ✓ Prevention of Obesity
- ✓ Prevention of Diabetes,pregnancy complications

Side effects of metformin: The most frequent side effect of metformin is stomach problems. Roughly 25% of people struggle with issues like:

- Diarrhoea
- Loss of appetite
- Stomach ache
- Metallic taste in mouth
- Nausea and vomiting
- Lactic acidosis
- Flatulence
- Asthenia

Rare side effects of metformin:

A small percentage of participants (less than 5% in one research) experienced headaches, upper respiratory infections, heartburn, or an unpleasant taste in their mouth after taking extended-release metformin. With the usual recipe, those negative effects affected up to 12% of users. In addition, they mentioned sweating, flushing, heart palpitations, rashes, and nail issues, along with flu-like symptoms.

Lactic acid accumulation is the harmful situation that results from the natural production of this molecule by your muscles and red blood cells. This condition is known as metformin-associated lactic acidosis (MALA) when it occurs while taking the drug.

The issue is extremely uncommon, occurring in a very small percentage of drug users.

It occurs mostly when you:

- possess liver or kidney disease
- Consume copious amounts of alcohol.
- Extremely severe cardiac failure from congestion
- Have a fever, diarrhea, or vomiting illness
- Lack fluids

Many of the warning indicators, like nausea, vertigo, and weakness, are comparable to certain metformin adverse effects. Other symptoms include heart rate fluctuations and limb numbness or coldness.

Contraindications:

Individuals with the following conditions should not use metformin:

• Severe renal impairment (eGFR < 30 mL/min/1.73 m^2)

• Acute or chronic metabolic acidosis, including diabetic ketoacidosis (from untreated diabetes), with or without coma.

• Known hypersensitivity to metformin

Drug interactions:

Cationic Drugs	Possess the ability to interact with metformin theoretically by vying for the same renal tubular transport mechanisms.
Carbonic Anhydrase Inhibitors	Reduce serum bicarbonate levels often, causing hyperchloremic metabolic acidosis and non-anion gap.
Drugs affecting Glycemic Control	Include phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, thyroid products, estrogens, thiazides and other diuretics, corticosteroids, phenothiazines, and isoniazid.

SAFETY:

One of the safest oral hypoglycemic medications is metformin.It lowers insulin resistance without increasing the risk of hypoglycemia since it does not stimulate β-cell insulin production.

Conclusion:

The anti-diabetic medication metformin hydrochloride is used to treat hyperglycemia. The recommended medication for the initial course of treatment for type 2 diabetes is metformin. Patients with type 2 diabetes can control their elevated blood sugar levels with the medication metformin in addition to diet. In order to reduce the quantity of glucose produced in the liver, lower the amount of glucose absorbed from the intestines, and increase insulin sensitivity, metformin is used.

When dietary therapy alone is unable to establish glycemic control in nonobese and obese patients with non-insulin dependent diabetes mellitus (NIDDM), metformin hydrochloride is just as effective as sulfonylureas. The ADA and IDF advise metformin as a promising candidate medication for the treatment of pre-diabetes, especially in individuals with combined IFG and IGT.159,160 Metformin use is becoming more popular in the treatment of insulin resistance conditions such PCOS, NASH, and HIV lipodystrophy syndrome.

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