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TYPE 2 DIABETICS MELLITUS CURED BY METFORMIN

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ABSTRACT

Metformin, a widely prescribed oral hypoglycemic agent, is used to treat type 2 diabetes by reducing appetite, inhibiting hepatic gluconeogenesis, and increasing glucose uptake by peripheral tissues. Metformin can prevent complications from high blood glucose but can negatively impact renal functions in T2DM patients, leading to chronic kidney disease. It can accumulate and cause lactic acidosis. Careful use is advised in elderly patients, those with trauma, fever, surgery, heart failure, or impaired kidney or liver functions. Moreover, the cost-effectiveness of metformin has been established. Generally, metformin is an excellent choice both in the specialized setting and in primary health care.

KEYWORDS: Diabetes mellitus, metformin, oral hypoglycemic agents, treatment, uses.

INTRODUCTION

Over the past 20 years, type 2 diabetes has become a major global health issue, affecting nearly 6% of the world's adults.[1] Metformin is an oral hypoglycemic agent that targets pancreatic cells, inhibiting hepatic glucose production and increasing insulin sensitivity in peripheral tissues. It reduces plasma insulin and glucose levels, enhances blood glucose control, and reduces diabetes-related complications.[2] Tolbutamide, glucose production, and insulin action in chlorpropamide, tolazamide, acetohexamide, glyburide, glipide, gliclazide, and cellular glimepiride reduce glucose levels by decreasing hepatic glucose production.[3] Metformin has been used as a first-line therapy in diabetes, but current guidelines suggest its use in people with a BMI between 25 and 59 kg/m2, higher fasting glucose (>110 mg/dL), higher A1C >6.0%, and patients with a propensity to cause gestational diabetes.[4] Galega officinalis, also referred to as the French lilac, is the source of metformin (1,1-dimethylbiguanide), a plant that has been utilized for millennia in traditional medicine.[5]

Galegine, an isoprenyl derivative of guanidine present in the perennial herb Galega officinalis—also referred to as goat's rue, French lilac, or Italian fitch—is the source of metformin. It was first utilized in European popular medicine throughout the Middle Ages. In the 1920s, galegine was investigated as a potential glucose-lowering medication in humans, but its short half-life and hypoglycemic mortality at high dosages proved to be too toxic.[6] Metformin and insulin together dramatically improve glycemic control, avoid weight gain, and lower the need for insulin, according to clinical research. During a 4-year follow-up period, one trial additionally examined cardiovascular end points. It found that the combination of metformin and insulin reduced the rate of events linked to macrovascular disease when compared to insulin alone.[7] Diabetes mellitus is currently often treated with the medication metformin. It is currently recognized as the first line of treatment for type 2 diabetes mellitus with lifestyle modifications due to its exceptional safety standards, efficacy, tolerability, and high hypoglycemia.[8] The only biguanide drug now available on the market is metformin, also known as dimethylbiguanide. Biguanides are compounds derived from Galega officinalis, often known as "goat's rue" or French lilac, a plant high in guanidine that was once used to treat diabetes mellitus because of guanidine's anti-hyperglycemic qualities. Despite the withdrawal of other biguanides, such as buformin and phenformin, due to a high occurrence of lactic acidosis, metformin remains the most commonly prescribed medication globally for the management of type 2 diabetes mellitus (T2DM).[9]

Synthesis

At 120–140°C for four hours, dimethyl amine hydrochloride and di-cyanodiamide are combined to create metformin subsists, with a 69% yield.

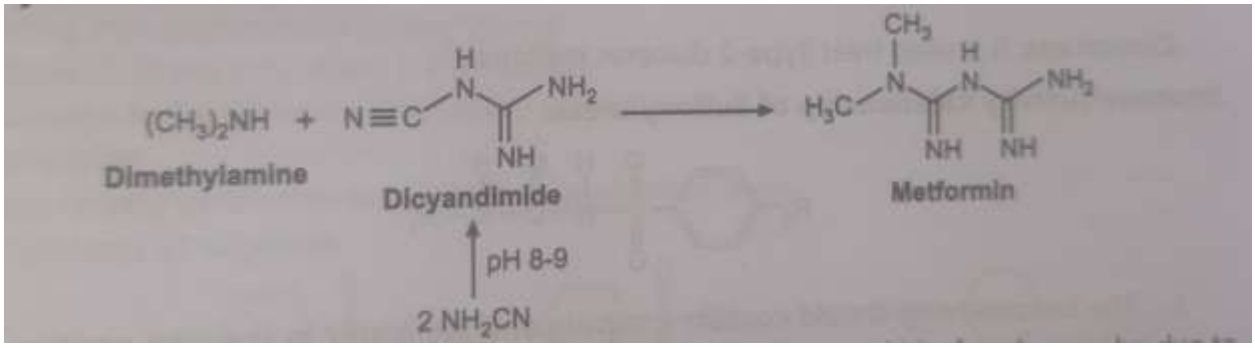
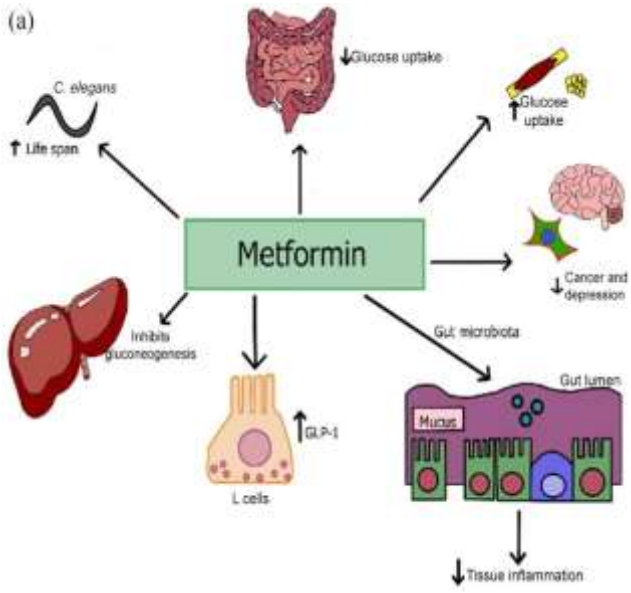


Fig. 2: Chemical reaction of Metformin.

1, 1-dimethylbiguanide hydrochloride, the coordination compound of metformin, is almost insoluble in acetone, scarcely soluble in ethanol, and easily soluble in water. The metformin pKa is 12.4. Metformin's traditional synthesis was first reported in 1922. A concentrated solution is obtained by dissolving equal molar quantities of dimethylamine and 2-cyanoguanidin in toluene by cooling them, as per the Aron patent procedure and the Pharmaceutical Manufacturing Encyclopedia. • Involves a one-pot reaction of hot dimethyl amine hydrochloride and 2-cyanoguanidin. Add the hydrogen chloride in equal moles at a time. The mixture began to boil on its own, and after cooling, a 96% yield of metformin hydrochloride precipitated. Figure illustrates how metformin is synthesized.[10]

Mechanism Of Action Of Metformin

Metformin also suppresses the endogenous glucose production by the liver, which is mainly due to a reduction in the rate of gluconeogenesis and a small effect on glycogenolysis. Moreover, metformin activates the enzyme adenosine monophosphate kinase (AMPK) resulting in the inhibition of key enzymes involved in gluconeogenesis and glycogen synthesis in the liver while stimulating insulin signaling and glucose transport in muscles. AMPK regulates the cellular and organ metabolism and any decrease in hepatic energy, leads to the activation of AMPK. This study to an extent has put forth to explain the mechanism of metformin action on liver gluconeogenesis.[11] Furthermore, metformin increases the peripheral glucose disposal that arises largely through increased non-oxidative glucose disposal into skeletal muscle. It usually does not cause hypoglycemia and this cause to be considered as a unique anti-diabetic drug.[12]



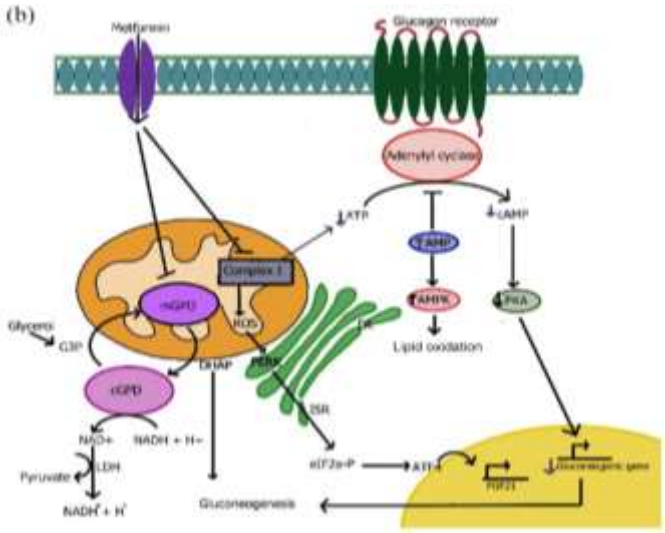


Fig: (A) Metformin improves glycemia by inhibiting hepatic gluconeogenesis, reducing absorption of glucose from the intestines, promoting glucose uptake by tissue, and increasing GLP-1 secretion. Additional benefits of metformin include alterations in the gut microbiota, reduction in inflammation, and reductions in cancer and depression. Metformin has also been shown to improve longevity in caenorhabditis elegans (C. elegans).[13] (B) Metformin diminishes mitochondrial complex I activity, resulting in decreased adenosine triphosphate (ATP) and increased adenosine monophosphate (AMP) content and activation of adenosine monophosphate-activated protein kinase (AMPK).[14]

The Impact of Metformin Therapy on Insulin Resistance and Expression of GLUT4

In current therapeutic use, metformin is a commonly prescribed insulin-sensitizing medication. Though it is most generally linked to lowering plasma glucose levels, our understanding of its unique qualities and impacts is still developing.[15] Its actions alter a number of biological processes. In terms of glucose homeostasis, insulin primarily functions by strengthening insulin-stimulated glucose disposal in peripheral tissues and insulin-mediated regulation of hepatic glucose synthesis; however, the exact molecular processes underlying these actions are yet unknown.[16] Metformin has been demonstrated in multiple trials in IR situations and study groups to enhance whole-body sensitivity to insulin by using different metrics for insulin sensitivity in people.[17] According to experimental research, metformin-mediated increases in insulin sensitivity may be linked to a number of processes, such as elevated glycogen synthesis, increased insulin receptor tyrosine kinase activity, and, most importantly, an increase in GLUT4 recruitment and activity. There are two ways to accomplish these effects: directly and indirectly.[18] Moreover, metformin may activate

adenosine 5′-monophosphate-activated protein kinase (AMPK), a so-called cellular energy sensor, via inhibiting mitochondrial complex I and other possible mechanisms.[19] Moreover, it can trigger the production of glucagon-like peptide-1, which increases insulin secretion and lowers plasma glucose levels.[20] Furthermore, further research revealed that the gut microbiota might be another target region.[21] Metformin has been shown in numerous studies to impact GLUT4 expression, translocation, and function; however, the underlying molecular mechanisms have not been elucidated. Metformin was found to mitigate the downregulation of GLUT4 in cultured rat adipocytes following continuous insulin therapy by Kozka et al. in 1993.[22] Metformin supplementation in the culture medium corrected insulin resistance (IR) caused by continuous insulin therapy in a related investigation on rat adipocytes.[23] Furthermore, GLUT4 expression in a combination of heart, liver, and visceral adipose tissues significantly increased and IR significantly decreased in rats with metabolic syndrome after a 4-week metformin treatment.[24] Metformin therapy enhanced insulin sensitivity in vitro and raised the expression of GLUT4 in skeletal muscle in diabetic animals using a similar experimental methodology.[25] An in vitro study found that long-term metformin exposure of cultured human myotubes was linked to a direct improvement in insulin action, which was also tied to higher expression of GLUT4 mRNA.[26]

Pharmacokinetics of Metformin

Absorption - Metformin is used orally in doses up to 2,550 mg/day, or around 35 mg/kg/day, in increments of 500 mg/b.i.d. or t.i.d. After an oral dose, the small intestine quickly absorbs the metformin formulation with immediate release. Its half-life in circulation is between 1.5 and 4.9 hours, and its duration of action is between 16 and 20 hours. Its start of action is approximately 1.5 hours.[27] The duodenum can absorb up to 20% of the whole dose, the ileum and jejunum up to 60%, and the colon only very slightly absorbs any of it. The remainder is expelled as feces.[28] Increased dosages decrease bioavailability and impede the rate of absorption.[29] Metformin appears to be fully absorbed in the gastrointestinal tract within 6 hours of administration, with an absolute oral bioavailability of 40 to 60%.[30]

Distribution - Plasma proteins do not bind to metformin.[31] Following intravenous injection, the volume of distribution (Vd) has been observed to range from 63 to 276 L. These numbers reflect Vd over the final 8–12 hours following an IV dose. (Table No.1)[32,33,34] The apparent volume of distribution following oral administration (Vd/F), which is calculated during multiple dosages, is more important. Vd/F is roughly 600 L when taking 2000 mg of

metformin once a day, either as immediate-release or sustained-release tablets (Table no.2).[34,35,36]

Table I. Pharmacokinetic parameters of metformin after intravenous administration

Parameter	Tucker et al.	Pentikäinen et al.	Sirtori et al.
Patients (n)	4	3	5
Dose (g)	0.25	0.5	1.0
Duration of collection of blood samples (h)	12	10–12	8
$t_{½}$ in plasma (h)[a]	4.5 ± 2.1	1.74 ± 0.19	1.52 ± 0.29
$t_{½}$ in urine (h)[a]	19 ± 10	8.9 ± 1.2	
CL (mL/min)[a,b]	706 ± 33	473 ± 18	441 ± 89
% of drug excreted unchanged[a]	78.9 ± 4.7	99.9 ± 1.4	86
V_d (L)[a,b]	276 ± 136	69 ± 8	63 ± 17

a Values are expressed as mean ± SD.

b $t_{½}$ and V_d estimated from plasma concentrations during the later times after dosage.

CL = apparent total clearance; $\mathbf{t_{½}}$ = half-life; $\mathbf{V_d}$ = volume of distribution.

Table II. Pharmacokinetic parameters of metformin during multiple-dosing regimens in healthy subjects (HS) or patients with type 2 diabetes mellitus (DM) with good renal function[a]

Dosage (mg)	n	C_{max} (mg/L)	$C_{av,ss}$ (mg/L)	CL/F (mL/min)	V_d/F (L)	$t_{½}$ (h)
Immediate-release						
HS, 250 mg bid	24	0.65 ± 0.11	0.35 ± 0.06	780 ± 139	NA	NA
DM, 850 mg tid	9	1.90 ± 0.63	1.35 ± 0.50	1118 ± 325	1952 ± 1519[b]	19.8 ± 15.9[b]
HS, 850 mg tid	9	2.01 ± 0.39	1.34 ± 0.35	1130 ± 457	1211 ± 690[b]	13.0 ± 7.8[b]
DM, 1000 mg bid	13	2.09 ± 0.56	1.23 ± 0.30	881 ± 215	NA	NA
HS, 1000 mg bid	15	1.32 ± 0.23	0.86 ± 0.19	1265 ± 274	559 ± 163	5.1 ± 1.0
DM, 850 mg bid[c]	12	NA	0.70 ± 0.06	1316 ± 113	648 ± 13.8	5.7 ± 1.1
Sustained-release						
HS, 500 mg od	16	0.60 ± 0.17	0.26 ± 0.08	1029 ± 325	463 ± 204	5.2 ± 1.6
HS, 1000 mg od	16	1.08 ± 0.26	0.52 ± 0.13	1033 ± 260	402 ± 123	4.5 ± 0.8
HS, 1500 mg od	15	1.44 ± 0.36	0.70 ± 0.17	1159 ± 287	481 ± 129	4.8 ± 0.5
HS, 2000 mg od	14	1.80 ± 0.29	0.85 ± 0.17	1271 ± 256	572 ± 175	5.2 ± 1.2

a Values are expressed as mean ± SD.

b V_d/F and $t_{½}$ are the pharmacokinetic parameters determined during the terminal log-linear phase elimination following termination of treatment and therefore do not represent the parameters over a dosage interval.

bid = twice daily; $\mathbf{C_{av,ss}}$ = average plasma concentration at steady state over a dosage interval; **CL/F** = total clearance after oral administration; $\mathbf{C_{max}}$ = maximum plasma concentration; **NA** = not available; **od** = once daily; $\mathbf{t_{½}}$ = elimination half-life; **tid** = three times daily; $\mathbf{V_d/F}$ = volume of distribution after oral administration.

Following an oral dose, the kidneys, adrenal glands, pancreas, and liver contain concentrations up to seven times the serum concentrations, with smaller amounts identified in the lung, muscle, and spleen. High concentrations of metformin in the urinary system may contribute to the high concentrations in the kidney, which are not always the result of absorption in kidney tissue.[37]

Metabolism - Metformin, a derivative of guanidine, the active ingredient in goat's rue, was historically used as a diabetes treatment in the Middle Ages.[38] The small intestine absorbs it in the digestive tract.[39] The drug's oral bioavailability ranges from 40% to 60%, with gastrointestinal absorption almost complete after 6 hours of oral administration.[40,41] The oral dose of metformin has been found to have a negative correlation with drug absorption, as it is rapidly distributed and excreted unchanged by the kidneys.[42] The plasma half-life of oral

administration typically ranges between 4 and 8.7 hours.[43] Metformin doesn't interact with other drugs, but anecdotal reports suggest it may be reduced by guar gum and α-glucosidase inhibitors, and increased by cimetidine in healthy volunteers.[40,44]

Elimination – Metformin is a hormone that is highly expressed in the liver, kidney, and skeletal muscle.[45] MATE1 may contribute to metformin excretion from the liver and kidney, but its role in hepatic secretion is questioned due to insignificant biliary excretion in humans. Metformin's plasma half-life is 2–6 hours, with a slower elimination half-life in erythrocytes, the gastrointestinal tract, and enterocytes, indicating absorption-limited kinetics.[46] Metformin's short plasma half-life makes significant accumulation unlikely, but erythrocyte accumulation may cause excess lactate production and potential lactic acidosis, especially when renal excretion is impaired.[47]

Drug interactions

Clinically significant drug interactions involving metformin are rare. Several medications, including cimetidine, frusemide, and nifedipine, can increase the concentration of metformin, potentially affecting its actions. Some medications excreted by renal tubular secretion, including morphine, quinine, ranitidine, digoxin, quinidine, amiloride, procainamide, triamterene, vancomycin, and trimethoprim, may be competing against metformin for elimination.[48]

Adverse effects

Metformin oral tablets can cause mild to serious side effects.[49] The typical side effects of this medication include nausea, abdominal pain, vomiting, diarrhoea, heartburn, headache, agitation, chills, dizziness, fatigue, abdominal cramps, loss of appetite, asthenia, myalgia, upper respiratory tract infection, and an altered taste.[49,50] The Diabetes Prevention Program and DPP Outcomes Study reveal that long-term metformin use is linked to vitamin B12 deficiency and anaemia.[51]

Contraindication

Diabetic Nephropathy (DN) is a microvascular complications.[52] Regarding metformin usage, abnormal kidney function is one of the main contraindications.The FDA guidelines in early 2016 prohibited metformin use in men with serum creatinine levels of 1.5 mg/dl or above and in women with levels of 1.4 mg/dl or above.[53] A study found that metformin usage in

patients with type 2 diabetes and advanced CKD increased the risk of all-cause mortality compared to those without metformin use.[54]

Therapeutic Uses

1. Metformin is effective in reducing body weight.
2. It is also used in polycystic ovary syndrome (PCOS).
3. It is used in cancer
4. It is used in type2 Diabetes.
5. It is used in pregnancy complications.

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