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# A Review: Pharmacovigilance & Metformin ADRs

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**ABSTRACT-**

Pharmacovigilance (PV) is an important field for patient safety and ensuring that the pharmaceuticals being consumed or injected are safe in every way.India is still in its infancy; there is much to be done and learned in the field of PV to ensure that the activities and work undertaken are carried out safely. The under-reporting of adverse medication reactions is a big issue in India (ADR). Patients are being admitted to hospitals in greater numbers as a result of drug side effects, and pinpointing the exact cause of ADRs becomes more difficult when a patient is taking multiple medications at the same time.Metformin (dimethylbiguanide) has become the first-line oral blood glucose lowering medication for type 2 diabetes management.Lactic acidosis, allergies, hypoglycemia, vitamin B12 insufficiency, changed taste, and gastrointestinal intolerance are the most common metformin side effects. Metformin should not be used if you have serious chronic conditions (such as hepatic, renal, or cardiac failure) or if you have diabetes complications (ketoacidosis and hyperosmolar state). Metformin, together with medical and nutritional therapy, is considered the first-line treatment in type 2 diabetic mellitus (T2DM) by all worldwide standards.

## Introduction-

The pharmaceutical science of pharmacovigilance (PV), commonly known as drug safety, is concerned with the detection, assessment, understanding, and prevention of adverse effects, particularly long-term and short-term side effects of medications. Medicines PV is an essential component of clinical research. A key setback is the under-reporting of adverse drug reactions (ADRs). This could be due to a lack of time and report forms all around the world. It has long been known that the World Health Organization (WHO) has taken steps to improve global health. The programme for reporting all drug-related adverse effects. Furthermore, the scope of its concerns has been expanded to cover herbal drugs, goods, customs. [1]

The term pharmacovigilance is derived from the Greek word Pharmacon, which means drug, and the Latin word Vigilare, which means to be awake or aware, to be on the lookout.[2]

Effective drug regulation systems, public health programmes, and clinical practice all require pharmacovigilance. It promotes the detection of previously unknown ADRs and interactions, as well as increases in the frequency of known ADRs, as well as identifying risk factors for the development of ADRs, estimating quantitative aspects of benefit or risk analysis, and disseminating information to improve drug prescribing and regulation. [3]

The practice and science of pharmacovigilance, which can be defined as the science of monitoring hazardous drug reactions, arose as a result of increased knowledge of adverse drug reactions. Detection, assessment, comprehension, and prevention of negative outcomes side effects or any other potential drug-related issues. It is well-known. Acknowledged that a medicine must go through several stages of clinical testing before it is marketed, it must undergo a clinical trial to determine its safety and efficacy. Commercially, Clinical studies, on the other hand, have a number of drawbacks. It can be utilised in a variety of ways, for example, stringent rules for inclusion and exclusion allow it to be used in a variety of ways. An extremely restricted selection of patients; population groups such as Children, pregnant women, and the elderly make up the majority of the population. The significance of pharmacovigilance is becoming increasingly important, as seen by recent high-profile drug withdrawals from the market by regulatory authorities, consumers, and others. Grown, and people are becoming more aware of the benefits and risks of drugs. [4]

Pharmacovigilance is a critical component of clinical trials. Throughout the product lifecycle, both clinical trial safety and post-market pharmacovigilance both are essential. While substantial advances in the field of pharmacovigilance have been made in Western countries, India has made little progress. There is a critical requirement to comprehend the significance of pharmacovigilance and how it affects the product's life cycle. This will allow for the incorporation of appropriate pharmacovigilance b into the processes and procedures, which will aid in regulatory compliance, clinical trial safety, and post-marketing surveillance.Pharmacovigilance is not a new concept in India; it has been practised since 1998. "An adverse event is defined as any untoward event that occurs as a result of the use of a drug. "Toward a medical event that may occur with medication treatment but may not require treatment "Its use must unavoidably have a relationship with it." "Any noxious, adverse drug reaction" is defined as "any unpleasant, adverse drug reaction. "Unanticipated and unwanted side effect of a medication that occurs at a human

dose Physiological function prevention, diagnosis, therapy, or change. Further Due to its vast population, high enrolment rate, and low cost, India is becoming a hotspot for clinical research efforts. Furthermore, the time between a medicine being initially introduced to the market in the United States, Europe, or Japan, or anywhere else in the world, and its subsequent availability in India has shrunk significantly. As a result, long-term safety data and the time of their marketing in India are not available for such pharmaceuticals. This is demonstrated by the fact that all of the recently withdrawn high-profile medications were available on the Indian market. In such circumstances, Indian regulatory agencies are unable to rely on the experience of other markets to assess the benefit-risk balance of a given product.Thereby emphasising the significance of India having its own well-designed pharmacovigilance system.The office of the Drugs Controller General of India (DCGI) has been working hard to put the National Pharmacovigilance Program (NPP) into action in India. A generic firm in India is primarily responsible for the following operations in order to fulfil its pharmacovigilance duties for its marketed medications, as per emphasizing. Pharmacovigilance aids in the prevention of negative medication effects: Since Hippocrates' time, medical research has advanced in leaps and bounds. Pharmaceutical medications of today are truly life-saving. .[5]

Pharmacovigilance is the expertise of collecting, observing, examining, assessing, and estimating evidence from health care workers and patients on the adverse effects of medications, natural products, herbal, and traditional treatments with the goal of:

•Identifying new dangers connected with treatment options.

•Infectious disease prevention and control in patients.

•Requirements for reporting under unusual circumstances.

Pharmacovigilance is an essential component of clinical research. Throughout the product life cycle, both clinical trial safety and post-marketing pharmacovigilance are crucial. [6]

The focus of pharmacovigilance is not just on pharmacological side effects, but also on polypharmacy, iatrogenesis, paradoxical reactions, and major adverse drug events.Pharmacovigilance is an essential and inseparable component of clinical trials. Clinical trials and post-marketing pharmacovigilance (also known as post-marketing studies or phase IV clinical trials) have a huge and critical impact on a product's life cycle. Because of the relatively large number of recent high-profile drug withdrawals, both the pharmaceutical industry and numerous regulatory authorities throughout the world have raised the bar.In terms of the Indian pharmacovigilance system, the introduction of a national pharmacovigilance programme has proven profitable for the field in terms of reporting ADRs, although with certain related abnormalities or lower strength when compared to other developed countries' pharmacovigilance systems.[7]

## What is pharmacovigilance & how does it work?

Before and after a drug is successfully tested and released on the market, it is necessary to monitor its effects. Pharmacovigilance entails the monitoring and evaluation of drug quality, as well as the detection and prevention of pharmacological side effects. Pharmacovigilance is the process of assessing information from health care providers, pharmaceutical firms, and patients in order to better understand the risks and benefits of a specific drug. Pharmaceutical companies invest millions of dollars and a significant amount of time in the research and development of new pharmaceuticals. They invest a significant amount of money on clinical trials before the drugs are approved and released on the market.It is widely acknowledged that information technology (IT) has penetrated and altered the field of health care and clinical medicine, allowing clinicians to perform their profession with greater quality, efficiency, and cost savings. It's also no secret that information technology has combined with clinical safety practise, resulting in the development of global pharmacovigilance platforms for safety signal identification.

Throughout the life cycle of a clinical product, regulators are expecting proactive surveillance programmes that comprise comprehensive risk management plans and signal detection/analysis.

•What exactly is pharmacovigilance, according to this?

•What do we know about its advantages and disadvantages?

•What obstacles stand in the way of its widespread adoption?

•What does the future hold for pharmacovigilance in the global medical community?

It is now widely agreed that part of the process of reviewing drug safety must occur in the post-marketing phases, with regulators having the final say on whether and how this should occur. The more robust national pharmacovigilance and adverse drug reaction (ADR) reporting systems are, the more probable rational regulatory decisions for the early release of novel medications with therapeutic potential will be made. Full safety monitoring is not limited to new medications or important therapeutic advancements, though. It plays an important role in the introduction of generic medications as well as the assessment of the safety profile of older drugs that are already on the market, when new safety concerns may have arisen. While spontaneous reporting remains a cornerstone of pharmacovigilance in the regulatory context and is critical for signal detection, the necessity for more active surveillance has grown. Spontaneous reports are unable to identify the frequency of an ADR attribution to a product or its safety in comparison to a comparator without information on usage and degree of consumption.To answer these critical safety problems, more systematic and robust epidemiological methodologies are needed, taking into account the limitations of spontaneous reporting and postmarketing investigations. They should be included in post-marketing monitoring programmes. This the utilisation of pharmacoepidemiologic studies is included.These actions are being carried out in order to identify adverse events and, to the extent possible, to comprehend their nature,

frequency, and potential risk factor. In theory, pharmacovigilance entails identifying and evaluating safety signals. Signals can be derived from post-marketing data as well as other sources, such as pre-clinical data and incidents linked to similar pharmacological classes.[8, 27]

## Aims of pharmacovigilance-

PV plays a key role in determining the severity of pharmacological side effects, whether they are produced by oral, parenteral, or intravenous medicines. Before being marketed worldwide, some medications are subjected to ADR testing. PV plays an important role in the assessment, detection, and identification of medications that induce ADRs and the mechanism by which they do so. However, it is the obligation of the doctors involved in the case to meet these requirements of discovering and eradicating a side effect; nurses, health workers, residents, and proper patient supervision aid to ease the root cause of ADR.[9] The main goals of pharmacovigilance are to demonstrate the efficacy of drugs by tracking their adverse effect profile for many years from the lab to the pharmacy; improving public health and safety in relation to drug use; encouraging the safe, rational, and cost-effective use of drugs; promoting understanding, education, and clinical training in pharmacovigilance; and effective communication to the generic public. [10]

• Investigate the efficacy of medications and track their side effects from the lab to the pharmacy and beyond for several years.

•Pharmacovigilance keeps track of any negative side effects that medications may have.

•Improve public health and safety when it comes to drug use.

•Contribute to the evaluation of a medicine's benefit, harm, effectiveness, and risk, promoting its safe, logical, and effective (including cost-effective) usage.

•Promote pharmacovigilance awareness, education, and clinical training, as well as effective public communication. [11, 26]

## Importance of pharmacovigilance-

It is the branch of science that deals with the difficult task of comprehending and describing the nature of adverse drug reactions (ADR) that occur in patients who are receiving either oral, parenteral, or intravenous (I.V) medications for a medical condition. Drugs on the market around the world have undergone a variety of testing, as well as clinical trials in animals and humans, to determine the drug's safety for a specific disease and to determine the exact side effects. Even so, a large portion of it escapes unreported, and some ADR are discovered via post-marketing surveillance. A considerable number of ADRs are expected to exist, lowering quality of life, lengthening hospital stays, and increasing death. According to a seminal research by Lazarou published in 1998, ADRs are the fourth to sixth greatest cause of death in the United States and ADRs are thought to be responsible for 3-7 percent of all hospital admissions. [12]

## Need of pharmacovigilance-

Reason 1- Inadequate evidence of safety from clinical studies is a humanitarian concern. Prior obtaining marketing approval, animal trials are subjected to phase 1-3 studies.

Reason 2- Medicine is designed to help people live longer and healthier lives. It is occasionally unavoidable to die from an illness; nevertheless, dying from a medicine is unacceptable.

Reason 3- The cost of ADRs to the country exceeds the cost of the drugs.

Reason 4- Advising on the proper use of medications and ensuring that they are taken as prescribed.

Reason 5- Keeping the public's trust.

Reason 6- Knowing information that is damaging to someone who is unaware of it and not telling them is unethical.[13]

Post-marketing surveillance is what pharmacovigilance is all about. Monitoring medications after they are marketed is necessary for a variety of reasons. Involvement factors can be divided into two categories:

(a) Human factors b) Post marketing topics

Among the human factors to consider are:

a) Insufficient evidence of safety from clinical trials due to their short duration, often only a few weeks.

b) During clinical trials, animal experiments frequently do not simulate human pharmacodynamics and pharmacokinetics.

I) During clinical trials, the population size is limited—no more than 5000 volunteers, and often as few as 500.

ii) The population segment is small and age and gender specific.

iii) The trials provide limited indications because only the specific disease is being researched.[14]

## Establishment of pharmacovigilance-

As a result of this horrifying epidemic, many countries established drug-safety agencies, such as our own committee on drug safety, and the WHO later established an International bureau in 1968 to collect and collate information from National Drug Monitoring Organizations. Since then, the WHO has taken up the mantle and is now playing a major role in spreading these programmes around the world. At the time, some western countries established spontaneous reporting schemes, which can be regarded as the first generation of progress in pharmacovigilance. Individual case reports of suspected ADRs are collected and stored in a common database, which currently contains over 3.7 million case reports. The WHO Programme, which was established in 1968, consists of a network of National Centres.[15, 25]

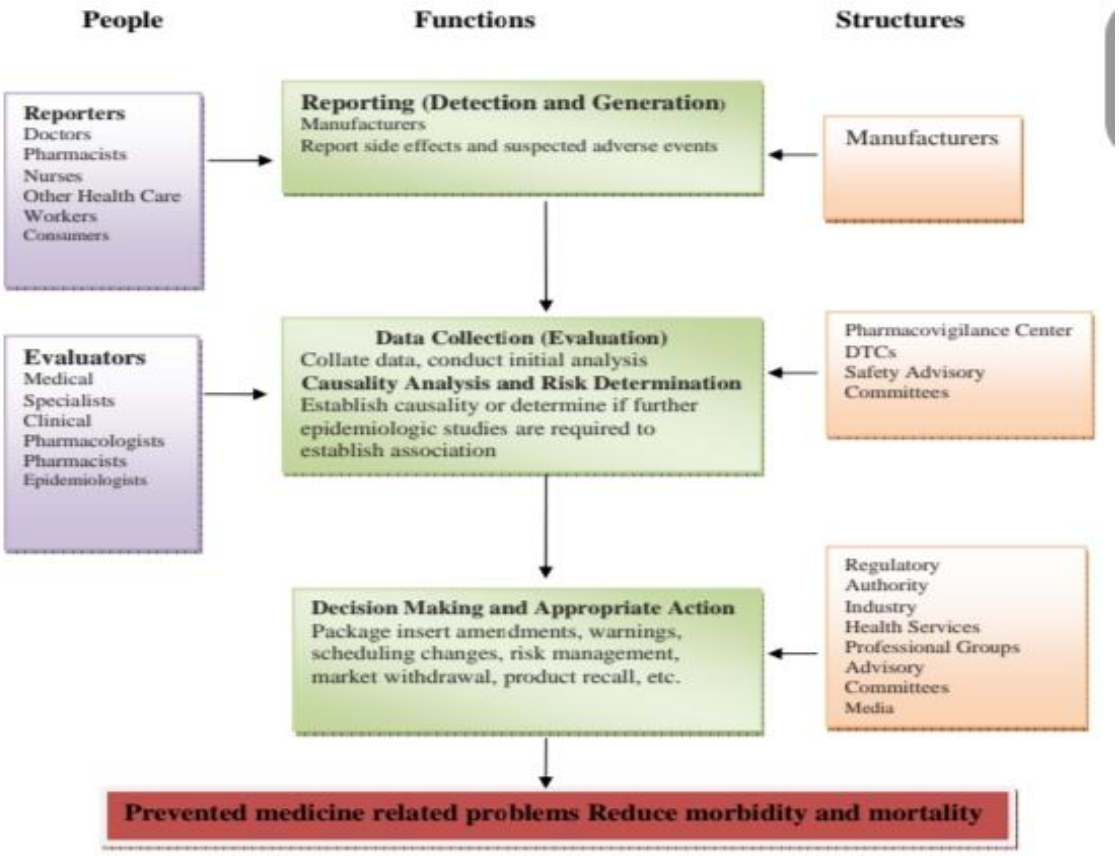


**Figure 1: The pharmacovigilance framework: relating people, functions, structures, and expected outcome and impact.**

**•Metformin**

**Chemical name of metformin-**

1,1-Dimethylbiguanide hydrochloride

**Molecular formula-**

C4H11N5

Metformin (dimethylbiguanide) has supplanted insulin as the preferred first-line oral blood glucose-lowering medication in the treatment of type 2 diabetes. Galega officinalis (also known as goat's rue) is a traditional herbal medication in Europe that was discovered to be high in guanidine, which was proved to reduce blood glucose in 1918. Metformin was unearthed in the 1940s while looking for antimalarial drugs, and during clinical trials, it was found to be effective in treating influenza while also lowering blood glucose. Metformin (1,1-dimethylbiguanide hydrochloride) has had a tumultuous history, from herbal heritage in Europe to synthesis and the discovery of its glucose-lowering effect in the

1920s: information that was overlooked and ignored. Metformin was uncovered in the 1940s while looking for antimalarial drugs and repurposed to treat influenza before being approved for the treatment of adult-onset diabetes in 1957.[16]

**Rise of metformin-**Phenformin and buformin were more effective than metformin and received higher acclaim and use at first, but their link to lactic acidosis caused them to be phased out in most nations by the end of the 1970s. Although metformin's reputation has been tarnished by its association with phenformin and buformin, growing research has verified the drug's antihyperglycemic efficacy without producing overt hypoglycemia or weight gain.

**The commercial side-**Aron Laboratories was acquired by Lipha Pharmaceuticals (now Merck), and in 1995, Dr Gerry Daniel, the US Chief Executive Officer, brought metformin to the United States, where it became a blockbuster under licence from Bristol Myers Squibb. Fixed combination pills containing metformin and other antidiabetic medicines have maintained metformin's appeal. Although much of this research predates the availability of current models of insulin resistance, many biguanides and similar guanidine derivatives have been investigated as potential anti-diabetic drugs. Metformin, on the other hand, has a favourable risk–benefit ratio due to its various modes of action and unique pharmacokinetic and pharmacodynamic features, making it a leading treatment for type 2 diabetic patients. Metformin, on the other hand, has a favourable risk–benefit ratio due to its various modes of action and unique pharmacokinetic and pharmacodynamic features, making it a leading treatment for type 2 diabetic patients. [17, 24]

**Figure 2 – Galega officinalis (goat's rue)l**

**•Mechanism of action of metformin-**

Metformin is typically assumed to improve blood glucose levels via acting on the liver, and multiple lines of evidence back this up. First, metformin was ineffective at improving blood glucose after high-fat feeding in mice lacking the organic cation transporter 1 (OCT1), which take up little or no metformin into the liver. Second, human tracer studies suggest that metformin reduces hepatic glucose synthesis while having no effect on peripheral insulin-mediated glucose uptake.

**Metformin and the mitochondrial control of hepatic gluconeogenesis-**

Hepatocytes must balance the demand for ATP with supply, which is predominantly provided by mitochondria, because gluconeogenesis is an energy-intensive process (using six ATP equivalents per mole of glucose synthesised). Because metformin has a positive charge, the membrane potentials across the plasma membrane and mitochondrial inner membrane (positive outside) force metformin into the cell and then into the mitochondria, resulting in concentrations up to 1000 times higher than in the extracellular media. Metformin's inhibition of Complex of the respiratory chain , which inhibits ATP production, is the most extensively studied mitochondrial activity. The high extracellular concentrations (mmol/l) required to observe rapid effects have been a persistent criticism of this mechanism, even though lower concentrations of metformin (50–100 mol/l) do inhibit Complex I in rat hepatoma (H4IIE) cells after several hours; this delay was attributed to the slow uptake of metformin by mitochondria, It was just discovered in an experiment. Furthermore, other investigations have found no changes in cellular ADP:ATP ratios after metformin administration, despite the fact that they can be seen with phenformin. Concurrent inhibition of this process in cells undergoing

gluconeogenesis could explain minor changes in ADP:ATP ratios. Other effects of respiratory chain inhibition besides ATP generation, such as alterations in the NAD+:NADH ratio, may potentially play a role in metformin's gluconeogenesis effects.

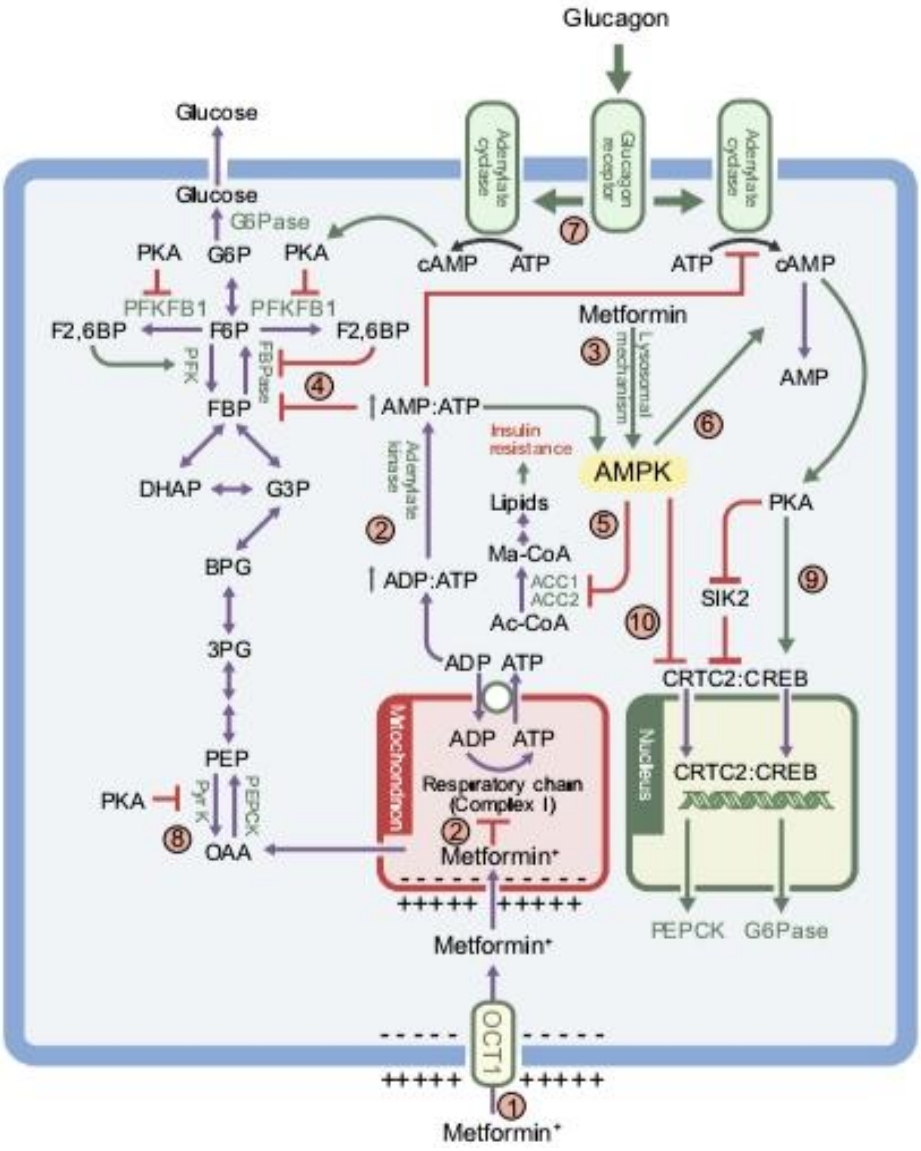


**Figure 3- multiple mechanism via which metformin affects liver metabolism**.

**Metformin mechanisms for metformin- associated AMPK activation-**

Metformin's capacity to stimulate the cellular energy sensor AMP-activated protein kinase can potentially be explained by mitochondrial function inhibition (AMPK).

AMPK functions to restore energy homeostasis by switching on catabolic pathways that generate ATP while switching off cellular processes that consume ATP once activated by increases in AMP:ATP and ADP:ATP ratios.Metformin could therefore activate AMPK through a mechanism involving the lysosome rather than the mitochondrion.

**AMPK-dependent and independent effects of metformin on hepatic gluconeogenesis**

5-aminoimidazole-4-carboxamide ribonucleoside (AICAR), a nucleoside that is taken up into cells and phosphorylated to the nucleotide 5-amino-4-imidazolecarboxamide riboside 5′-monophosphate (ZMP), which mimics all effects of AMP on the AMPK system, was the first

pharmacological AMPK activator to be developed.Initially supported the theory that metformin's ability to decrease hepatic glucose synthesis was due to AMPK activation.In hepatocytes from control mice or mice lacking both AMPK catalytic subunits in the liver, acute treatment with metformin or AICAR suppressed glucose production equally well, while metformin acutely increased glucose tolerance in both mouse strains. Metformin increased the cellular AMP:ATP ratios in hepatocytes , which is consistent with respiratory chain inhibition. As a result, AMP may have an extra AMPK-independent effect, lowering cAMP and inhibiting gluconeogenic enzyme expressions.

**Metformin and the intestine-**

Metformin increases anaerobic glucose metabolism in enterocytes, resulting in lower net glucose absorption and increased lactate transport to the liver, which has long been thought to be a target organ for the drug. Metformin's activities on the intestines could affect glucose metabolism in a variety of ways, according to certain theorie. A recent mouse study found that colonic FDG uptake was not enhanced after 48 hours of metformin administration, but was increased after 30 days of treatment, an effect that lasted even after metformin was stopped for 48 hours. In rats, a route linking duodenal metformin exposure to inhibition of hepatic glucose production via the nucleus tractus solitarius and vagal efferents, via AMPK and GLP-1 receptor activation (gut–brain–liver crosstalk) was discovered.

**Metformin intolerance-**

Metformin medication is frequently linked with gastrointestinal adverse effects (20–30% of patients), with severe side effects leading to metformin cessation in 5% of patients. The mechanism by which metformin induces gastrointestinal side effects is unknown. There are a number of possible mechanisms; for example, the side effects could be due to the high concentration of metformin in intestinal enterocytes, which could explain why slow-release metforminformulations, which disperse slowly and reduce local luminal metformin concentrations, reduce GI intolerance.[18,23]

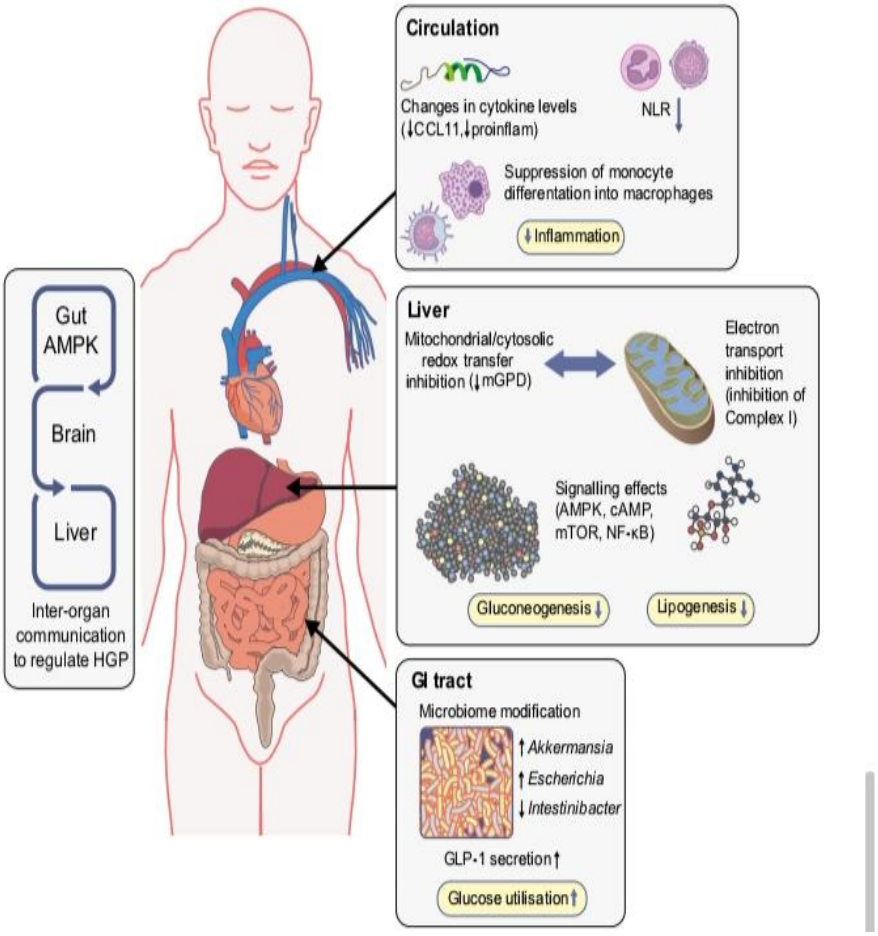


**Figure 4 – Action of metformin on metabolism and inflammation**

**•Pharmacological actions of metformin-**

**Metformin as antidiabetic agent-**

Metformin is the most often given medicine for type 2 diabetes globally, either alone or in combination with insulin or other glucose-lowering therapy. Metformin was similarly pulled off the market in the United States because to worries about lactic acidosis, but it was returned in 1995 after being demonstrated safe and effeective.

**Mechanism of action-**Metformin acts in the liver, where it suppresses gluconeogenesis by inhibiting a mitochondrial redox shuttle, according to animal and human research. However, a complete knowledge of metformin's mechanism of action is still a work in progress, and the drug's effects are likely to be pleiotropic. Metformin, for example, has been proven to be an insulin sensitizer with numerous modes of action in the gut lumen.

**Clinical use -** Metformin is used to treat hyperglycemia in people with type 2 diabetes and improves glycemic control without causing hypoglycemia or weight gain (Figure). 3,4 A randomised clinical trial of intensive vs. conventional glycemic management among individuals with newly diagnosed type 2 diabetes supports the use of metformin. In a subgroup of overweight patients randomly assigned to metformin (n = 342) versus conventional (diet) therapy (n = 411), this trial demonstrated lower rates of myocardial infarction (7 percent absolute risk reduction; P =.01) and mortality (7.1 percent absolute risk reduction; P =.01).

**Safety**-Metformin has essentially no safety risks based on sixty years of clinical practise and trial data. Metformin, on the other hand, induces subclinical elevations in lactic acid and appears to cause lactic acidosis in severe overdose. Metformin is not recommended for people with lactic acidosis risk factors such as hepatic impairment, heart failure, or chronic renal disease (CKD). However, long-term experience with metformin suggests that it is only dangerous for a tiny proportion of people with severe liver, heart, or renal disease. [19]

**Metabolic disorder-**

During clinical trials, this hypoglycemic medication has been found to exhibit a variety of pleiotropic metabolic effects. Metformin's glucose-lowering impact is mediated by AMPK, which is also involved in lipid metabolism regulation. AMPK phosphorylates and inactivates acetyl-Co-A carboxylase, which is required for rate-limiting fatty acid synthesis. Metformin monotherapy at 1500 mg/day has been proven to lower total cholesterol, triglycerides, LDL-C, and VLDL-C while increasing HDL-C levels. Overweight people were studied in a small research to see how metformin affected lipid peroxidation in the event of a myocardial infarction and mortality from any cause.

**Cardiovascular disease-**

Metformin is the only antidiabetic medicine that has been found to improve macrovascular outcomes, most likely due to its non-glycemic effects. A sub-analysis of obese individuals treated extensively with metformin in one of the largest trials—the United Kingdom Prospective Diabetes Study (UKPDS)—found that they had a 33 percent lower risk of myocardial infarction than people treated conventionally.Over a ten-year period of follow-up, overweight patients showed a sustained reduction in microvascular risk, as well as a lower risk of myocardial infarction and mortality from any cause. This impact was considered to be attributable to metformin's pleiotropic properties, rather than only glycemic control.

**Inflammation-**

Chronic low-grade inflammation is a major ageing factor, and addressing inflammatory mechanisms has shown promise as a means to prolong human life and prevent age-related disorders.Metformin reduces IL-1b-induced production of the pro-inflammatory cytokines IL-6 and IL-8 in human vascular smooth muscle cells (SMCs), macrophages, and endothelial cells (ECs) in a dose-dependent manner, according to human cell data.

**Cancer-**

In T2DM patients, there is a proven elevated risk of specific cancer forms. T2DM has been linked to an increased risk of liver, pancreas, endometrial, colorectal, breast, and bladder cancer in numerous studies and metaanalyses.An analysis of 9 retrospective cohort studies and 2 randomised controlled trials for possible effects of metformin on pancreatic cancer patient survival revealed a substantial improvement in survival in metformin-treated patients compared to control patients.A meta-analysis of 11 trials that included 5464 BC patients with diabetes (2760 patients who had received metformin and 2704 patients who had not) found that metformin has a preventive effect against breast cancer (BC) in postmenopausal diabetic women. [20, 22]

## •Adverse reaction of metformin-

**1.Lactic acidosis-**

In the 1970s, two strong biguanides, phenformin and buformin, were used to treat type 2 diabetes. The Swedish Adverse Drug Reaction

Committee examined reports involving biguanides from 1965 to 1977. (0.6 percent of the total).

The fact that phenformin was given in 6% of the cases where the patient died (the bulk of which were due to lactic acidosis) drew notice. Following the analysis of the committee report, the class was used with caution, and metformin was preferred over phenformin because an early study found that type 2 diabetic patients admitted to the hospital had a higher mean lactate level when they were treated with a different medicine than the one mentioned earlier.

A Cochrane meta-analysis published in 2006 evaluated data from 206 trials and cohort studies and found no cases of lactic acidosis in either metformin-treated or control patients. Furthermore, although there was a modest difference between patients treated with this biguanide and those treated with phenformin, the lactate level was not significantly enhanced in the metformin group.

Lactic acidosis was found to be 391/100.000 person-years among patients treated with metformin in a case-control study of 10.652 Danish type 2 diabetic patients, although the medicine alone did not increase the risk; concomitant conditions were more important.

**2.Allergic reaction (infrequent)-**

Metformin causes very few systemic allergic responses. It can be used in hypersensitive asthma patients without raising the risk of adverse effects such as hospitalizations, asthma-related emergency room visits, or exacerbations. Despite the fact that cutaneous allergic responses are rarely described, doctors should be aware of their occurrence.

**3. Hypoglycemia (very rare)-**

Metformin was found to be safe and effective in monotherapy as a first-line agent in a recent meta-analysis. The risk of hypoglycemia was reduced than with sulfonylurea monotherapy.

There have been a few reported cases of older people with comorbidities and polypharmacy (angiotensin-converting enzyme inhibitors or nonsteroidal anti-inflammatory medications) or malnutrition.

**4. Vitamin B12 defeciency-**

Potential vitamin B12 deficiency should be considered and checked in type 2 diabetes patients who have been on high-dose metformin (more than 2 g/day) for a long time [59], according to the American Diabetes Association Guidelines. The metformin-treated group had a considerably reduced level of this vitamin, according to a meta-analysis of 29 trials. The medicine competes with vitamin B12 absorption and inhibits intrinsic factor action, according to the implied processes.Because it changes bowel movement, it causes bacterial overgrowth.

**5. Altered taste-**

The buildup and excretion of metformin in saliva can induce taste disruption as a side effect. The salivary glands exhibit large levels of the organic cation transporter-3 (OCT3), which is responsible for metformin transportation and could be involved in the pathogenesis of this adverse effect, according to Lee N et al. Metformin uptake in the saliva was downregulated in OCT3(/) mice in animal experiments.

**6. Gastrointestinal intolerance ( widespread)-**

Diarrhea, nausea, meteorism, and constipation are among of the gastrointestinal side symptoms that afflict about 20% of individuals.

Metformin hydrochloride is normally taken orally and is absorbed mostly via the small intestine. Drug transfer by organic cation transporter 1 (OCT1) allows the concentration inside the enterocyte to reach up to 300 times that of the circulation Metformin also boosts glucose utilisation in the anaerobic cycle and lactate generation in the enterocyte. A local increase in lactate production could be linked to negative effects.

Metformin decreases the absorption of bile acids, resulting in osmotic diarrhoea, according to Scarpello et al. After a 500-mg dose of metformin, the serum levels of lactate, serotonin, and bile acids were similar in normal and intolerant participants, leading the authors to infer that the intolerance is most likely due to local variables within the lumen or enterocyte. Some researchers speculated that diminished OCT1 function could affect metformin tolerance in the digestive tract. Metformin intolerance was also more common in the cohort with reduced-function OCT1 alleles. The danger was elevated considerably higher if this cohort was also given an OCT1 inhibitor. As a result, individuals who are taking other drugs that interact with OCT1 may be at a higher risk of gastrointestinal ADR.

There are numerous formulations available, including immediate-release (IR) tablets with a high local concentration, extended-release (XR) tablets with a prolonged discharge of the active molecule due to a dual polymer matrix, and delayed-release tablets with a delayed release of the active molecule (DR). The XR and DR forms aid in the consistent distribution of molecules across the intestinal barrier, which helps to reduce intolerance.

**7. Hypothyroidism (controversial)-**

Metformin works by triggering the enzyme adenosine monophosphate-activated protein kinase (AMPK), which also activates thyroid iodine in vitro. Metformin was thought to affect thyroid function as a result. Metformin treatment reduced only T3 levels in healthy individuals, but not iodine uptake, TSH, or fT4 levels.

Observational studies supported this notion, demonstrating that metformin treatment reduced thyroid-stimulating hormone (TSH) levels, while randomised control trials failed to confirm this concept.[21,22]

## •Conclusion-

PV continues to be a vibrant aspect of physicians' and the general public's lives. It is critical that these adverse drug effects be reported and investigated as soon as possible once they emerge. Not only should doctors be informed of the PV programme, but so should patients, so that self-reporting is raised and the burden on clinicians is lessened. India is still in the early stages of PV, and more reporting is required to meet the international standard for reporting adverse events in order to ensure safe drug use in children and pregnant women, who are among the most susceptible populations. Metformin is the most extensively prescribed oral hypoglycemic medication, with a lengthy history of use in the treatment of type 2 diabetes. 12–14 Anorexiogenesis, reduced intestinal carbohydrate absorption, suppression of hepatic gluconeogenesis, and enhanced glucose uptake by peripheral tissues are among its key mechanisms of action.Despite its tumultuous past, metformin is still the most commonly prescribed medication for the treatment of type 2 diabetes. To avoid gastrointestinal side effects, progressive dose increases should be encouraged. If the patient does not have any other serious comorbidities, lactic acidosis isn't necessary. Metformin's indications have now expanded to include oncology, endocrinology, and gastroenterology, providing the scientific community with more information concerning the drug's side effects.

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