A Review on Metformin for the Treatment of Type II Diabetes Mellitus

By

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A thesis submitted to the Department of School of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy

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Declaration

It is hereby declared that

1. The project submitted is my/our own original work while completing degree at Brac University.
2. The project does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The project does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis titled “A Review on Metformin for The Treatment of Type II Diabetes Mellitus” submitted by Muhammad Tasnim Yasin (18346072), of Spring, 2019 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (hons.).

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Ethics Statement

This study does not involve any human or animal trial.

Abstract/ Executive Summary

Metformin, a well-known medication for type 2 diabetes, has demonstrated promise in postponing or averting the disease's beginning in high-risk patients. The first line of treatment for type 2 diabetic mellitus is biguanides like metformin. They function well both on their own and in combination with other medications that decrease blood sugar. For T2DM control, aggressive treatment is required to fulfill targets for cardiovascular risk factors and blood sugar levels. In this context, in addition to its antihyperglycemic properties, metformin—an established and widely used first-line medication—stands out for its capacity to ameliorate endothelial dysfunction, hemostasis and oxidative stress, insulin resistance, lipid profiles, and fat redistribution. Its mode of action involves decreasing insulin resistance, raising insulin sensitivity, and lowering the quantity of glucose the liver produces. The medication is useful in lowering blood glucose levels without raising the risk of hypoglycemia, according to a large body of research. It is generally highly received, reasonably priced, and has little side effects. Despite metformin's therapy is widely used and effective, there are still significant drawbacks and difficulties with it, including gastrointestinal side effects, individual differences in response, and issues with using it in particular patient populations. With significant advantages in glycemic control and other areas, one of the cornerstones of type 2 diabetes treatment remains to be metformin. It's vital position in the arsenal against Type 2 Diabetes and associated problems is reaffirmed by ongoing research efforts that uncover its varied therapeutic potential and enhance its clinical efficacy. Diabetes, metformin, glucose, insulin, biguanides, hypoglycemia.

Keywords: Diabetes, metformin, glucose, insulin, biguanides, hypoglycemia

Dedication

I would like to dedicate this manuscript to my parents.

Acknowledgement

First and foremost, I would like to express my gratitude to Allah for all of his blessings, which have given me the perseverance and determination to complete this project. I would like to take this opportunity to thank my academic supervisor, Dr. Sabrina Sharmin (Assistant Professor at the School of Pharmacy at BRAC University) for her guidance and encouragement while writing this manuscript. Throughout my studies and project writing, she was a true source of support and motivation. Lastly, I want to express my gratitude to my family for constantly inspiring me to step beyond of my comfort zone. I could not have made it this far without my family's and loved ones' constant support and prayers.

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List of Acronyms

T2DM	Type 2 diabetes mellitus
B1 (LKB1)	Liver Kinase B1
AMPK	Adenosine monophosphate-activated protein kinase
CREB	Cyclic AMP-Responsive Element-Binding Protein
TORC2	Target of Rapamycin (TOR) complex-2
GLP-1 RA	Glucagon-like peptide 1
SGLT-2	Sodium-glucose cotransporter-2
EASD	European Association for the Study of Diabetes
ADA	Americans with Disabilities Act
UGDP	The University Group Diabetes Program in united states
CYP2D6	Cytochrome P450 family 2 subfamily D member 6
AGEs	Advanced glycation end products
NADPH	Nicotinamide adenine dinucleotide phosphate
ROS	Reactive oxygen species
MDA	Measuring malondialdehyde
TBARS	Thiobarbituric acid reactive substances
8-Isp	8-isoprostane
IR	Insulin resistance
8-OHdG	8-hydroxy-2' -deoxyguanosine

FADH2	Flavin adenine dinucleotide
ETC	Electron transport chain
ATP	Adenosine triphosphate
IRS-1	Insulin receptor substrate 1
mtDNA	Mitochondrial DNA
TRAF2	Tumor necrosis factor receptor-associated factor 2
NFKB1	Nuclear factor kappa B subunit 1
OXPHOS	Oxidative phosphorylation
CVD	Cardiovascular disease
ADP	Adenosine diphosphate
cAMP	Cyclic adenosine monophosphate
mTORC1	Mammalian target of rapamycin complex 1
TSC2	Tuberous sclerosis complex 2
CRTC2	Coactivator regulated transcription coactivator 2
GPD2	Glycerol 3-phosphate dehydrogenase
PON1	Paraoxonase-1
VCAM-1	Vascular cell adhesion molecule 1
ICAM-1	The intercellular adhesion molecule
PMAT	Plasma membrane monoamine transporter
MATE1	Multidrug and toxin extrusion

GDM	Gestational diabetes mellitus
NICE	The National Institute for Health and Care Excellence
SGLT2	Sodium-Glucose Transport Protein 2
TZDs	Thiazolidinediones
DPP-4	Dipeptidyl peptidase 4
OHAs	Oral hypoglycemic agents
IGT	Impaired glucose tolerance
RCTs	Randomized controlled trials
CKD	Chronic kidney disease

Chapter 1

1.1 Introduction

For many years, the mainstay of treating type 2 diabetic mellitus (T2DM) has been metformin (1,1-dimethylbiguanide). The French lilac, or Galega officinalis, is the source of the medication, which was initially discovered in 1918 to have glucose-lowering properties. It is a member of the biguanide drug class. (Patel & Mundi, 2019). When phenformin became available in 1957, this class of drugs was utilized in order to manage type 2 diabetes. The International Diabetes Federation recommendations were published in 2005, and metformin was named the initial course of treatment for diabetes type 2 (T2DM) following its FDA approval on December 29, 1994, based on encouraging trial results (Verma & Mehendale, 2022). Metformin primarily reduces the synthesis of glucose in the liver. Moreover, it improves the uptake of glucose by peripheral tissues, particularly muscle. Liver kinase B1 (LKB-1), an upstream kinase that controls the downstream enzyme adenosine monophosphates protein kinase (AMPK), is activated to produce these effects (Patel & Mundi, 2019). The transcriptional co-activator Transducer of Regulated CREB Protein 2 (TORC2) is phosphorylated by AMPK. As a result, it becomes inactive, which in turn suppresses transcriptional activities that promote the production of gluconeogenic enzymes. It has also been proposed that suppression of mitochondrial respiration contributes to the reduction of gluconeogenesis since it reduces the energy supply required for this process (Baker et al., 2021). Because of its effectiveness, safety record, positive effects on the heart and metabolism, and ability to interact with other antidiabetic medications, metformin is a highly recommended medication (Rojas & Gomes, 2013). The first line of treatment for type 2 diabetic mellitus is biguanides like metformin. They function well both on their own and in combination with other medications that decrease blood sugar. It has few negative effects, is generally highly tolerated,

and is fairly priced. Although the safety and efficacy of metformin have been established, there is disagreement on whether patients should always receive this medication as their first prescription, since other anti-hyperglycemic medications have been found to offer notable benefits in some patient populations. Before changing anything in clinical practice, it is critical to understand the benefits and drawbacks of metformin and other anti-hyperglycemic medications (Baker et al., 2021).

1.2 Type 2 Diabetes Mellitus

Diabetes mellitus is a chronic metabolic condition characterized by persistent hyperglycemia, often caused by reduced insulin production or insulin resistance (Bailey, 2017). The organ systems may be damaged as a result, posing a risk to life and necessitating the management of microvascular and macrovascular illnesses by an interprofessional team (Goyal et al., 2023). Type 2 diabetes mellitus (DM) is a long-term metabolic disease that is becoming more and more common worldwide. Because of the aging population, the disease is predicted to increase in the next ten years, which will put more strain on healthcare systems, especially in less developed nations. Treatment options available today include insulin sensitizers like metformin, oral hypoglycemic medications, weight management, and lifestyle changes. Novel drugs including insulin-releasing glucokinase activators and glucagon-like peptide 1 analogs have been developed as a result of recent research (Olokoba et al., 2012). Obesity and type 2 diabetes mellitus (T2DM) are connected worldwide health problems that increase the risk of microvascular and macrovascular consequences (Goyal et al., 2023). Insulin resistance and other abnormalities are influenced by genetic and environmental factors. It needs more than one antidiabetic medication to maintain normoglycemia and enhance quality of life. New drugs are being developed to improve insulin sensitivity, stop β-cell failure in the pancreas, and

prevent or treat microvascular problems (DeFronzo et al., 2015). Hyperglycemia and reduced insulin sensitivity are hallmarks of type 2 diabetes mellitus (T2DM), a complicated metabolic illness. Currently accepted explanations include liver malfunction, adipocyte dysfunction, pancreatic β-cell failure, and muscular defects. The cause is complex, but two important factors are genetic predisposition and physical inactivity. The pathophysiology of the disease has been studied in animal models, and novel treatments have been developed (Lin & Sun, 2010).

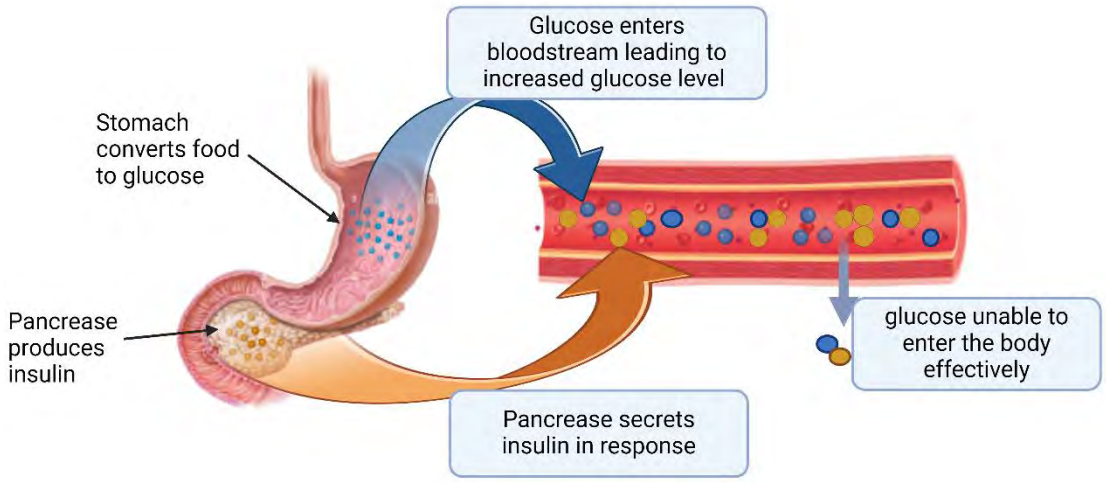

Figure 1: Formation of Type 2 Diabetes [Drawn using BioRender]

1.3 Use as First Line Therapy

For type 2 diabetes, metformin is a commonly used first-line treatment that works well either taken alone or in combination with other drugs (DeFronzo et al., 2015). However, due to a lack of convincing evidence and limited data on cardiovascular outcomes, its safety and effectiveness are under question. Recent data from glucagon-like peptide-1 receptor agonist and sodium-glucose cotransporter-2 inhibitor trials have changed diabetes care guidelines. Following a diabetes diagnosis, metformin should be started as soon as possible. In high-risk individuals, newer glycemic-lowering drugs should be taken into consideration (Ahmad et al.,

2020). When choosing a course of therapy, cost is still a major consideration (Baker et al., 2021c). Patients diagnosed with type 2 diabetes now have access to eleven different medication classes and insulin formulations. Patients have to make decisions based on expenses, advantages, risks, and quality of life. For many years, metformin hydrochloride has been the recommended initial treatment (Good & Pogach, 2018). Since its FDA approval in 1994, metformin has been the go-to medication for treating type 2 diabetes because of its reduced cost, weight neutrality, and improved glycemic control. Nonetheless, newer GLP-1 RA and SGLT-2 inhibitor outcome trials have changed diabetic treatment recommendations. The EASD suggests that patients with comorbidities should take these drugs into consideration, however the ADA Standards of Care recommends metformin as first-line therapy. Until more information is obtained, the discrepancy in the best course of care for high-risk individuals will not be resolved (DeFronzo et al., 2015). The goal should be to increase the number of people using the best medications for cardiovascular health (Baker et al., 2021d). Because of its advantages in reducing cardiovascular mortality, metformin, the most popular glucose-lowering medication, is the first-line treatment for newly diagnosed type 2 diabetes (T2D). Metformin's significance in the treatment of type 2 diabetes has been called into question, nevertheless, by recent large cardiovascular outcomes trials that used SGLT2i and GLP-1RA. Revisions to treatment algorithms are currently recommended by experts in order to improve glycaemic management and target atherosclerotic cardiovascular disease (Ahmad et al., 2020).

1.4 Aims and Objectives

This review article focuses on the pharmacodynamics and pharmacokinetics of metformin, its uses in the treatment of type 2 diabetes. Additional uses of metformin and its uses in

combination therapy are discussed in this article. Other potential uses of metformin and its adverse effects are also taken into account.

The purpose of this study is

-To elaborately discuss the mechanism of action of metformin

-To explore its current uses

-To discuss additional uses and benefits in combination therapy

-To highlight its adverse effects

-To outline its potential uses other than treating type 2 diabetes

Chapter 2

Methodology

The information was obtained from peer reviewed journals, research papers, articles available in databases such as PubMed, Frontiers, Springer, MDPI, ScienceDirect, Google Scholar and so forth. Significant keywords such as diabetes, metformin, glucose, hypoglycemia was used to search literatures. On the basis of the topic, relevant and useful articles were gathered, and further context was investigated. After deciding on a theme, an outline was prepared with appropriate headings and subheadings. Mendeley Desktop provided the bibliography and in-text citations. The entire essay was paraphrased, and the writing included citations.

Chapter 3

Historical Overview of Metformin

3.1 Herbal History

The herbal ancestry of metformin originated in medieval Europe, where Galega officinalis, also called professor weed, goat's rue, French lilac, Italian fitch, and Spanish sainfoin, was utilized as a traditional remedy (Kaneto et al., 2021). In Hill's, Galega officinalis—also referred to as Herba rutae caprariae in various herbals—was suggested as a remedy for frequent urination and thirst. It was commonly acknowledged in Europe that wild G. officinalis was its name comes from the fact that it is an animal galactagogue. (Milk stimulant is Greek). The plant was brought to North America in 1891, and many states consider it to be a noxious weed. G. officinalis was discovered to be rich in guanidine and similar chemicals in mid-1800s chemical investigations, particularly in the immature seed pods (Mestrovik, 2011). Animal blood glucose levels were found to be lowered by guanidine in 1918. Several monoguanidine derivatives, In the 1920s, it was also shown that diguanide's, such as synthalin (two guanidine's separated by a methylene chain) and glargine (isoamylene guanidine), could lower animal blood glucose levels. This resulted in the development of galegine and the more effective synthetic as diabetic therapies; however, as toxicity was discovered, early hope was dashed, and their usage was discontinued in the 1930s as insulin became more generally accessible (Bailey & Bailey, n.d.).

3.2 From Galega to Biguanides

The synthesis of guanidine by Strecker and the combination of the pair of guanidine's to generate biguanide by Rathke are the chemical sources of metformin (Tahrani et al., 2007). The first reports of Biguanides, including metformin lowering animal blood glucose did not

appear until 1929. However, because large doses were needed for even a slight reduction in blood glucose in animals without diabetes, its potential was not fully realized (Bailey, 2017).

3.3 Rediscovery via Malaria and Influenza

The separate creation of proguanil (Paludrine), a third thread in the history of metformin was the development of an antimalarial medication based on guanidine in the middle of the 1940s.Research on animals revealed that this medication lowered blood glucose levels (Davis, n.d.-b). In an effort to discover substitute guanidine-based antimalarials, proguanil was changed to metformin. In 1949, Eusebio Garcia tested the antimalarial efficacy of metformin in the Philippines and found that it effectively treated a local influenza outbreak. As a result, metformin hydrochloride was created and marketed as flumamine, an anti-influenza drug. However, it was soon observed that metformin was also known to lower blood sugar levels in certain influenza patients (Yanuar, 2017).

3.4 Step forward Jean Sterne

Aron Laboratories doctor Jean Sterne was the visionary who made metformin's antihyperglycemic potential a clinical reality. Sterne and Denise Duval embarked on a comprehensive research program in 1956 to investigate the pharmacodynamics of medications based on guanidine, such as metformin and phenformin, in animals with normal and diabetic blood (Shurrab & Arafa, 2020b). They found that in both normal and diabetic animals, metformin had little side effects and that in certain patients with maturity-onset diabetes, it might take the role of insulin. It did not, however, remove the requirement for insulin in patients with juvenile onset. In 1957, Sterne released a seminal study demonstrating that metformin was oral and hypoglycemic in a variety of animals. In order to promote metformin, he also proposed the term "Glucophage" (glucose eater). Sterne was a major contributor to continuing research and training of physicians (Bailey, 2017).

3.5 The Biguanide Opportunity

Phenformin was discovered in 1957 as a result of the discovery and publication of guanidine derivatives in the 1950s. But because phenformin is more effective at decreasing blood sugar levels in people with human maturity-onset diabetes than sulphonylureas, it has become a popular option around the world (Nasri & Rafieian-Kopaei, 2014). Both buformin and metformin were not approved for use in the USA and were only sporadically used in Europe. In the long run, metformin and sulphonylureas produced comparable glycemic control without causing appreciable hypoglycemia or weight gain. Subsequent research revealed the necessity for renal monitoring, reduced baseline insulin concentrations, and improved hemodynamics. (Bailey & Bailey, n.d.).

3.6 Lactic Acidosis

Especially with buformin and phenformin, the possibility of lactic acidosis was a major worry, especially after phenformin was removed from the UGDP study in the United States in 1971 (Perez, 2024). In Europe, taking buformin and phenformin were stopped in 1978, while metformin users experienced fewer cases. However, the fact that metformin was linked to other biguanides damaged its reputation, and lactic acidosis was brought on by a mutation in the CYP2D6 hydroxylation enzyme (Bailey, 2017).

3.7 Metformin Enters The USA

Following Lipham Pharmaceuticals' 1986 acquisition of Aron Laboratories, the FDA and sponsor conducted a comprehensive reevaluation of metformin. Drs. Gerard Daniel and Anita Goodman headed the Lipha team, which put in a lot of overtime to develop clinical trials and respond to FDA inquiries. The FDA approved metformin in 1994, and later clinical research expanded upon and validated the findings of Edinburgh. In order to ensure the drug's safe introduction, Bristol Myers Squibb purchased the US marketing rights and launched an

education effort (Davis, n.d.). The program highlighted the drug's distinct mode of action from sulphonylureas and included warnings about renal impairment and hypoxemic situations. With increasing prescriber confidence, in 2000, new fixed-dose combinations of metformin and other oral glucose-lowering medications, such as sulphonylureas, were accessible, along with the approval of an extended-release formulation (Bailey & Day, 2004).

3.8 Metformin in the 21st Century

By the end of the 20th century, metformin's ability to safely lower blood glucose levels in diabetic patients had become well recognized on a global scale. The most often given oral anti-hyperglycemic drug in 2002 was metformin. Guidelines from the International Diabetes Foundation were published in 2005, recommending metformin as the first line of treatment for those with type 2 diabetes (Shurrab & Arafa, 2020). Nearly 50 years after the drug's rediscovery, the World Health Organization included metformin to its list of essential medications in 2011.Over the past ten years, a large number of clinical trials have evaluated in detail the risks associated with metformin-induced lactic acidosis in patients who have congestive heart failure, liver and renal impairment, or both. For the great majority of patients, metformin is a safe and effective medicine, according to the results of such research. In actuality, there is no longer a restriction on the use of metformin in individuals with reduced kidney function. (Baker et al., 2021).

Chapter 04

Mechanism of Action

4.1 Type 2 Diabetes and Oxidative Stress

Oxidative stress can be brought on by hyperglycemia through a number of mechanisms, such as glucose autoxidation, the generation of products from advanced glycation ends (AGEs), and the activation of enzymes such as NADPH oxidase (Kasznicki et al., 2014). ROS overproduction may also be influenced by elevated levels of free fatty acids, leptin, and other circulating factors in individuals with Type 2 Diabetes. One of the main sources of ROS production is mitochondria. When the free amino groups of proteins attach to the ketone or aldehyde groups of glucose, Schiff-bases, Amadori products, and AGEs are produced. Owing to their brief half-lives within cells and tissues, reactive oxygen species (ROS) and changes in their levels are challenging to assess in clinical settings (Ginns, 2018b). The redox status of humans has also been assessed by other techniques, such as measuring malondialdehyde (MDA), thiobarbituric acid reactive substances (TBARS), or 8-isoprostane (8-Isp). Lipid peroxidation is the background for ROS-mediated protein changes, such as glutathionylation, nitrosylation, carbonylation, and glycation. Type 2 diabetes (T2D) and insulin resistance (IR), two conditions linked to oxidative stress, are characterized by hyperglycemia and dyslipidemia. In various organs, aberrant lipid metabolism can exacerbate insulin resistance and compromise insulin signaling. When it comes to diabetes, ROS should be considered both dangerous agents and a necessary component of several biological reactions, such as insulin secretion, insulin sensing, and peripheral organs' uptake of glucose. In the skeletal muscle, muscular contraction is a significant source of ROS generation, and possible regulators such as exercise related Ca2+, AMPK, ROS, and NO signaling in diabetes individuals. Studies conducted both in vitro and in vivo have demonstrated the antioxidant qualities of statins, lipid-lowering medications.

They enhance superoxide dismutase in erythrocytes, lower plasma amounts of oxidized-LDL and protein-bound tyrosine's, and shield endothelial cells from oxidative damage. Regarding their impact on plasma tocopherols, there are disagreements. Certain studies indicate that individuals with statins have reduced levels of 8-OHdG and greater levels of vitamin E. (F et al., n.d.)

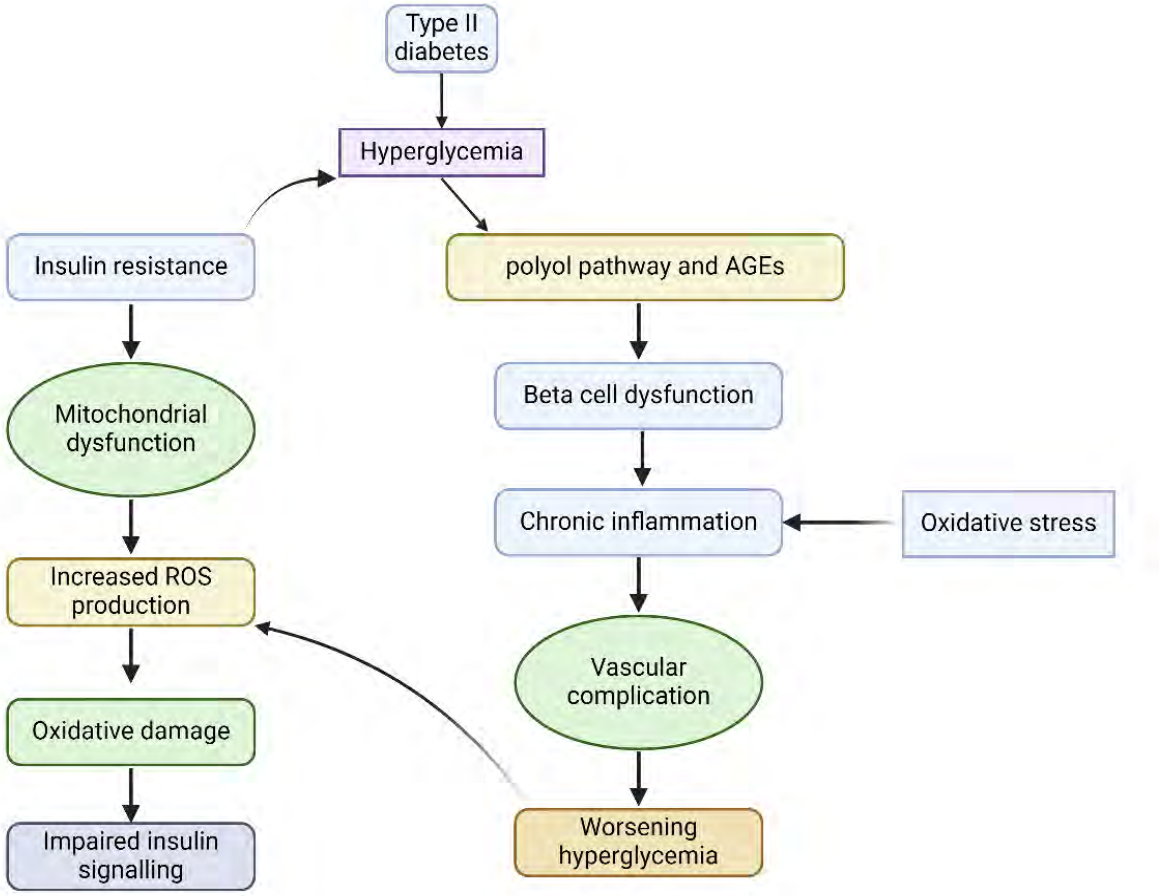

Figure 2: The interaction between type 2 diabetes and oxidative stress [Flowchart made using BioRander]

4.2 Diabetes Type 2 and Mitochondrial Malfunction

Mitochondria have a crucial role in the etiology of Type 2 Diabetes (T2D). ROS production is intimately associated with both mitochondrial malfunction and oxidative stress. Hyperglycemia and hyperlipidemia cause increases in glucose and lipid metabolism, which

raise NADH and FADH2 levels (Lv & Guo,2020). The mitochondrial electron transport chain (ETC) needs these two molecules to create ATP. The production of reactive oxygen species (ROS) by mitochondria can lead to the phosphorylation of IRS-1 by ROS, which can disrupt insulin signaling. There is a connection between oxidative stress, ROS generation, and mitochondrial dysfunction. Research has demonstrated reduced mRNA expression of genes linked to oxidative phosphorylation (OXPHOS) in muscle mitochondria under IR circumstances, as well as impaired OXPHOS in diabetic patients and their first-degree relatives. Because mitochondria are vulnerable to both environmental and genetic stressors, knowledge of the frequency of diseases linked to mitochondria, such as type 2 diabetes, can be aided by the accumulation of mtDNA mutations and their depletion (WebMD, 2019). The development of disease is linked to novel features of mitochondrial biology, including mtDNA heteroplasmy, non-coding RNA activities, epigenetic alterations, and epitranscriptomic regulation. Beyond abnormalities in the insulin signaling cascade, there is increasing interest in understanding the genes and mechanisms that cause insulin resistance (IR). As a molecular link between the two systems, TRAF2 and NFKB1, two potent candidates, are linked to mitochondrial and insulin genes. The development of T2D and IR-related disorders is significantly influenced by mitochondrial dysfunction, which is reliant on elements such as OXPHOS and mitochondrial dynamics. (Rena et al., 2017).

4.3 cardiovascular disease and type 2 Diabetes

Diabetes is a multisystemic disease that affects different organs in different ways. T2D is made worse by oxidative/nitrosative stress, including ROS and RNS, which are important in organs such the liver, adipose, muscle, and pancreatic islets (Ginns, 2018). Among other conditions related to metabolism and circulation, patients with type 2 diabetes are more likely to develop retinopathy, neuropathy, nephropathy, vascular diseases, and cardiomyopathy. Among T2D patients, CVD is a significant cause of morbidity and mortality. The development of vascular

disease and endothelial dysfunction is influenced by endoplasmic reticulum stress, autophagy, oxidative stress, and mitochondrial ROS generation, all of which are linked to hyperglycemia. (Kaneto et al., 2021).

4.4 The Molecular Processes by Which Metformin Works

The main effect of metformin is to inhibit the synthesis of glucose in the liver; however, because of its prolonged use at supratherapeutic dosages in in vitro and animal investigations, its secondary actions are contentious (Shortsleeve, 2024). Responses from cells and tissues differ according to dosage and length of therapy. Phenformin is an analog of metformin that was taken off the market in the 1970s because of concerns about lactic acidosis and increased cardiac mortality. It has been utilized in numerous investigations. Although phenformin has distinct properties, its activities are comparable to those of metformin (Rena et al., 2017).

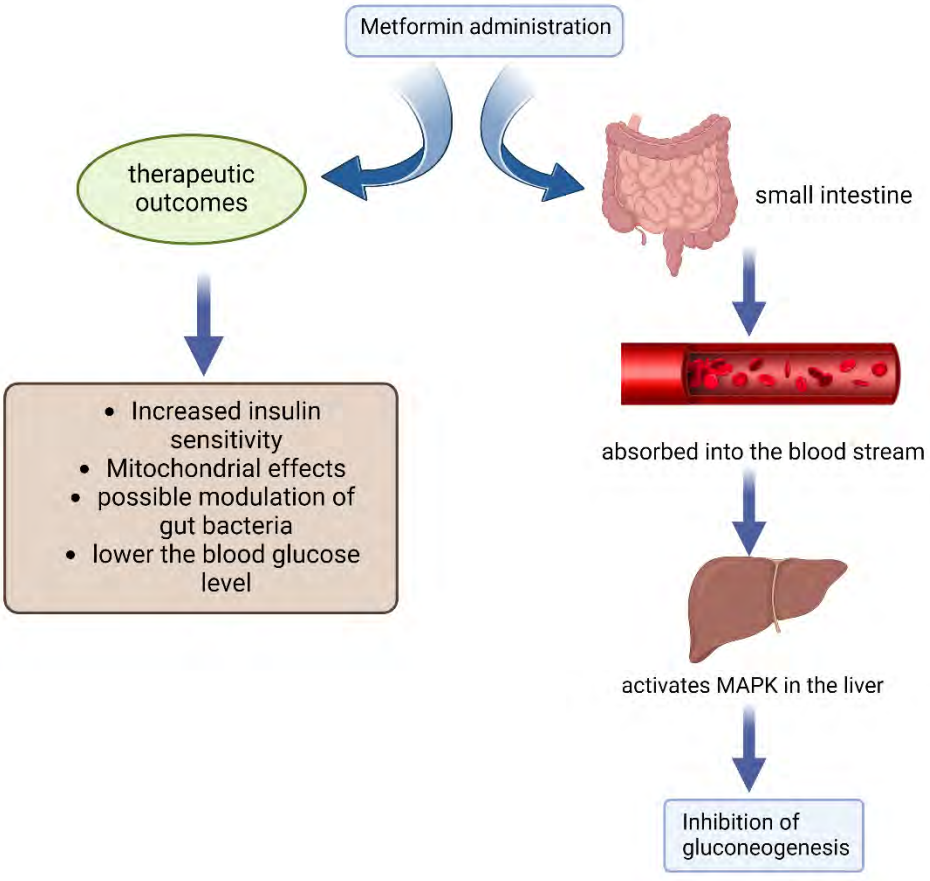

Figure 3: Mechanism of action of Metformin [Figure drawn by BioRender]

4.5 Metformin and Gluconeogenesis

The hepatic effect of metformin is thought to stem from its suppression of ATP generation in the mitochondria, which raises AMP and ADP levels in cells and modifies the AMP/ATP ratio. This results in the activation of AMPK, a bioenergetic sensor found in eukaryotic cells, which inhibits energy-consuming anabolic pathways like gluconeogenesis and encourages catabolic events (Soliman et al., 2020). However, some research indicates that metformin reduces glucose synthesis without changing ATP levels or the AMP/ATP ratio, casting doubt on the idea that bioenergetic stress is the fundamental mechanism underlying the drug's activities. Decreased cAMP levels inhibit the cAMP-PKA pathway, which may lessen the activation of AMPK (Foretz et al., 2023).

4.6 Activation of AMPK

Metformin stimulates AMPK, an essential regulator of hepatic glucose production, by phosphorylating the AMPK catalytic α subunit at Thr172 in primary hepatocytes. This activation is mediated by constitutive serine/threonine kinase LKB1, which may do so via promoting LKB's binding to AMPK. The anabolic process of glucose synthesis is regulated by the cAMP response element-binding (CREB) co-activator complex. AMPK activation inhibits this process (Khokhar et al., 2017b). The nuclear exclusion and phosphorylation of TORC2, the transcriptional coactivator CREB-regulated transcription coactivator 2 (CRTC2), are likewise encouraged by metformin-activated AMPK. AMPK's absolute necessity for the metformin-induced inhibition of glucose synthesis is debatable, though, as evidence of AMPK-independent activities has been mounting for some years (Mahmood, 2021).

4.7 Inhibition of mTORC1

The mTORC1 pathway, which controls translation and protein synthesis, is impacted by metformin. The GTP exchange factor for Rheb, tuberous sclerosis complex 2 (TSC2),

negatively regulates mTORC1 during starvation (Khokhar et al., 2017). Metformin inhibits the mTORC1 complex in both AMPK-dependent and -independent ways. AMPK-dependent techniques involve phosphorylating Raptor and activating TSC2, whereas AMPK-independent strategies involve situating the mTORC1 complex in late endosomes/lysosomes (Apostolovaa,b et al., 2020).

4.8 Metformin and Mitochondria

Metformin interferes with mitochondria, which are necessary for the energy-intensive process of gluconeogenesis, which is why it has hepatic effects. Metformin's modest, temporary, and selective suppression of complex I (NADH:ubiquinone oxidoreductase) in the respiratory chain is its most well-studied mitochondrial activity (Sadeghi et al., 2020). Complex I is rapidly inhibited within minutes of incubating isolated mitochondria with metformin at mM doses. It is yet unclear how metformin affects complex I activity, though. While some argue that it hinders a rate-limiting process associated with ubiquinone reduction, others point to the 49 kDa subunit on the matrix side that contains the ubiquinone binding site. It's uncertain how much metformin interferes with complex I. Metformin's hydrophilic nature and limited permeability via lipid membranes raise questions about its ability to enter and accumulate inside mitochondria (Jorquera et al., 2020). Although there are a number of transporters that can carry it, such as OCTs and MATE transporters, none have been found to be particularly effective in moving metformin through the intracellular medium (IMM). Metformin may build up within mitochondria, where it may reach concentrations up to 1,000 times higher than in the extracellular media, according to certain studies. Nonetheless, the accumulation of metformin in mitochondria has been questioned due to its lengthy half-life in vivo and wide apparent volume of dispersion. Furthermore, contrary to what some investigations have shown, metformin accumulates twice as much in the liver and does not depolarize isolated mitochondria. The drug's effects on metabolism are caused by its direct binding to

mitochondrial copper ions and its non-competitive suppression of mitochondrial glycerol 3-phosphate dehydrogenase (GPD2). This results in decreased glucose synthesis, decreased cytoplasmic NAD+/NADH ratio, and poor breathing. Metformin can bind to GPD2 without going through the IMM because of its position. Nevertheless, this process has been called into question due to factors like its lack of significance in hepatocytes, the unchanged nature of lactate-driven gluconeogenesis, and the somewhat reduced fasting blood glucose levels observed in GPD2 deletion animals (Foretz et al., 2023).

4.9 Metformin as a Promoter of Antioxidant Actions

In addition to diabetes, metformin has been demonstrated to have antioxidant properties in other pathophysiological contexts, including liver damage, cerebral ischemia, Parkinson's disease, and organ failure brought on by sepsis. Despite the fact that it has little antioxidant activity, it is important to comprehend the molecular mechanisms underlying its antioxidant activities (Hyer et al., 2018). Metformin has been demonstrated to downregulate NADPH oxidase, decrease intracellular reactive oxygen species (ROS) levels, and reverse oxidative stress in the mitochondria of rat pancreas. It also restores PON1 activity. Through a number of processes, such as the direct trapping of hydroxyl radicals, the enhancement of the endogenous antioxidant system, and the downregulation of NADPH oxidase, it plays an antioxidant effect (F et al., n.d.)

4.10 Metformin and Leukocyte-endothelium Interactions

Endothelial dysfunction and atherosclerosis are linked to type 2 diabetes. Leukocytes adhere to blood arteries in atherosclerosis through the action of adhesion molecules such as VCAM-1, ICAM-1, and selectins. Because of its anti-inflammatory and antioxidant qualities, metformin has been used to treat T2D and CVDs. It also lowers blood glucose levels (Verma & Mehendale, 2022). Increased leukocyte-endothelium interactions, decreased antioxidant

content, increased proinflammatory cytokines, and increased ROS generation can all be caused by hyperglycemia and IR. Through the AMPK-PARP1 cascade, metformin can decrease the polymer's action (ADP-ribose) polymerase 1 (PARP1) and increase phosphorylation of Enos and Akt, hence modulating the effect of hyperglycemia on endothelial function. The atherosclerotic process and CVD are avoided by this cardio vascularly beneficial action. ICAM-1, VCAM-1, and E-selectin are examples of soluble adhesion molecules that are important in leukocyte-endothelium interactions. The protective effects of metformin on leukocyte-endothelium interactions, mitochondrial activity, oxidative stress, and endothelial function may avert atherogenic processes and vascular damage in type 2 diabetes (Apostolovaa,b et al., 2020).

Chapter 5

Pharmacokinetic Profile

Metformin is a medication that passes through the urine unaltered since it is not processed. The kidney's active tubular secretion is the main method of elimination. The medication is absorbed by the kidney, liver, and intestines via organic cation transporters. There is observed individual variation in the pharmacokinetics of metformin (Brunmair et al., 2004). While intestinal absorption may be mediated by plasma membrane monoamine transporter (PMAT), OCT1 and maybe OCT3 are the primary mediators of hepatic uptake. Furthermore, metformin is a substrate for human multidrug and toxin extrusion 1 (MATE1) and MATE2-K, which may aid in metformin excretion from the liver and kidney. However, MATE1's role in hepatic secretion is still unknown. Metformin absorption into renal epithelial cells is mostly attributed to OCT2, which is expressed in the basolateral membrane of renal tubules. Renal excretion is mediated by MATE1 and MATE2-K, which are expressed in the renal proximal tubule cells. PMAT and OCT1 might potentially be involved in metformin reabsorption in renal tubules (Saleh et al., 2009). Genetic polymorphisms affect metformin pharmacokinetics and pharmacological reactions, and medication-drug interactions through blocking metformin transporters are clinically relevant. Proton-pump inhibitors, oral antidiabetic medications, and cimetidine may reduce the absorption of metformin, according to recent drug-drug interactions. Certain tyrosine kinase inhibitors and metformin may interact through transporters, which could have a clinical impact on the medication's toxicity, effectiveness, and disposition (Gong et al., 2012).

5.1 Absorption

Metformin is an oral medication available in dosage forms of 500 mg/b.i.d. or t.i.d. to 2,550 mg/day or 35 mg/kg/day. Its immediate-release version has a half-life of 1.5–4.9 hours and an onset of action of 1.5 hours, which is promptly absorbed by the small intestine (Stafford &

Elasy, 2007). Feces are the means by which any remaining medicine is removed. Metformin has a 40–60% oral bioavailability and a 6-hour gastrointestinal absorption period. The extended-release variant has a half-life of 6.5 hours and activates for 24 hours (Sheleme, 2021a).

5.2 Distribution

Although metformin enters the body quickly, it slows down to enter a deep compartment. It builds up in the kidneys, salivary glands, stomach, duodenum, and esophagus, among other organs. Over the course of 24 hours, it raises the blood-plasma metformin concentration ratio without binding to plasma proteins (Scheen, 1996a).

5.3 Metabolism

The half-life of metformin is roughly five hours, and its renal clearance is 510±120 ml/min. It is eliminated unaltered in urine. Metformin is mostly excreted from the body by the kidney by active tubular secretion (Ponssen et al., 2000). Low molecular weight, the existence of renal transporters, and low lipid solubility are factors that lead to high clearance. Renal function decline is directly correlated with decreased metformin clearance. It should not be started in patients who are older than 80 years old, and it is contraindicated in those with elevated blood creatinine levels or irregular clearance (Sheleme, 2021b).

5.4 Excretion

With a plasma elimination half-life that varies from 1.5 to 4.5 hours following intravenous injection and from 2.0 to 6.0 hours following oral administration in healthy volunteers, metformin is a drug that is rapidly excreted by the kidneys (Hougen et al., 2021). An additional terminal elimination phase that involves just a tiny portion of the injected dose and has a half-

life of 8 to 20 hours is indicated by the urine results. An increasingly reliable indicator of accurnulation is total clearing (Scheen, 1996b).

5.5 Therapeutic Monitoring

Rats administered metformin may experience higher incidence of minimal necrosis, body weight loss, and clinical symptoms, as well as morbidity and toxicity. Suicidal use is uncommon, although large overdoses might result with lactic acidosis. Patients with moderate-to-severe renal impairment typically have higher metformin levels in their plasma (Rojas & Gomes, 2013b). The FDA recommends against using the medicine in patients with an estimated glomerular filtration rate (eGFR) of less than 30 mL/min/1.73 m2. Elderly people should have their creatinine clearance rate evaluated before to use. Impaired hepatic function may make it more difficult to remove lactate, so drinking too much alcohol should be avoided. The common symptoms of gastrointestinal intolerance, which include diarrhea, flatulence, and abdominal pain, can be resolved with enough calcium. Megaloblastic anemia is rarely linked to a vitamin B12 deficiency (Sheleme, 2021c).

5.6 Drug Interactions

Through pharmacokinetic factors, metformin's low protein binding and lack of hepatic metabolism lessen the possibility of pharmacological interactions with phenformin and sulphonylureas (Scheen, 1996c). Strong base metformin is absorbed, dispersed, and eliminated via a variety of transporters, including as plasma membrane monoamine transporters, multidrug and toxin extruders, and organic cation transporters. These transporters mediate its hepatic uptake and absorption. Medication that blocks Metformin transporters can raise plasma concentrations of the drug, reduce its excretion, and raise the risk of lactic acidosis. Medication interactions are rare because metformin is not digested (Lavernia et al., 2015b). Certain cationic agents may compete with metformin for elimination. Among the drugs that are clinically

significant include cimetidine, contrast agents, dolutegravir, preprohormone, pyrimethamine, ranolazine, rifampicin, St. John's wort, trimethoprim, vandetanib, and verapamil (Sheleme, 2021d).

Chapter 6

Treatment

6.1 Metformin and Pre-diabetes

People with increased blood glucose levels, known as prediabetic persons, are susceptible to type 2 diabetes. Similar to long-term consequences from diabetes, this syndrome, also known as high-normal fasting plasma glucose or oral glucose tolerance, can cause damage to both the macro- and microvasculature. Reduction of β-cell activity and insulin sensitivity are key components in the prevention of type 2 diabetes. Pharmacological therapies, bariatric surgery, and lifestyle modifications can all help lower the chance of development. In general, metformin is safe and well-tolerated (Hostalek et al., 2015). Higher-than-normal blood glucose levels are the hallmark of prediabetes, a condition of intermediate glucose dysregulation between normal glucose tolerance and overt diabetes. It impacts 298 million adults and 464 million adults between the ages of 20 and 79. Diabetes and cardiovascular disease mortality rates are two illnesses that have been connected to prediabetes. Because prediabetes raises the chance of developing other health conditions, it is imperative to find effective therapies to either delay or avoid the transition from prediabetes to diabetes (Patel et al., 2023). Metformin has been shown to be an effective, safe, and cost-efficient treatment for prediabetes in high-risk people. Those who fit the DPP eligibility requirements and those who are most at risk—younger people, obese people, people with high blood sugar, or people who have gestational diabetes mellitus—should be prescribed it. Prompt and intensive therapy can postpone hyperglycemia, avert complications, and enhance long-term well-being (Herman & Ratner, 2020).

6.2 Metformin in the Treatment of Adult Individuals with Diabetes

Almost 10% of individuals globally suffer from type 2 diabetes, which is a leading cause of illness, mortality, disability, and expensive medical expenses. The focus of management has switched from glucose to focused complications and etiology (Kim et al., 2019). Improvements in patient-centered care concentrate on medication and non-pharmacological strategies to lower risks and address how social determinants of health affect the management of hyperglycemia (Galindo et al., 2023). Patients with gestational diabetes mellitus (GDM) may benefit from metformin and insulin therapy for better maternal and perinatal outcomes. Metformin and insulin were found to have comparable effects on glycemic control in a meta-analysis encompassing eight trials. However, because to the lack of long-term effects in children, insulin continues to be the recommended medication for managing hyperglycemia throughout pregnancy. Diabetes Poland advises PCOS-afflicted women to stop taking metformin. Metformin is used to treat women with PCOS who have metabolic abnormalities, decreased glucose intolerance, and irregular menstrual cycles. Since it also improves the fibrin features in Type 2 Diabetes Mellitus (T2DM) by lowering platelet activity, oxidative stress, and improving endothelial function, it may be used as a treatment for cardiovascular problems (Gonzalez-Lopez & S. Wojeck, 2023). Metformin is currently not recommended as the first line of treatment for all individuals with type 2 diabetes, even though it is a commonly used background medicine in trials looking at cardiovascular and kidney outcomes. Instead, it is suggested that cardiac and renal comorbidities be considered while selecting a course of treatment. When choosing the best course of therapy, cost is a key factor that needs to be taken into account. Unfortunately, US insurance has not kept up with these recommendations. For patients with cardiac or renal comorbidities, the National Institute for Health and Care Excellence (NICE) continues to suggest metformin as the initial line of treatment. In cases where a patient is unable to take metformin or requires more intensive treatment, an SGLT2i

is recommended. In some cases, a medication other than metformin may be used as a first-line therapy for symptoms or severe hyperglycemia (Galindo et al., 2023b).

Chapter 7

Use in Combination Therapy

The American College of Endocrinology and the American Association of Clinical Endocrinologists recommend dual therapy for patients whose HbA1c readings are greater than 7.5%. For patients without hyperglycemia, oral glucose-lowering medications are advised. If the desired HbA1c isn't reached after three months, the European Association and the American Diabetes Association for the Study of Diabetes advise combining two medications. Combination medication, like hypertension and hyperlipidemia, is the best course of action for many people. Individualized treatment plans for type 2 diabetes should take patient preference, cost, risk-benefit analysis, and efficacy into consideration (Matthews et al., 2020). This method offers potential benefits over sequential treatment and targets pathophysiologic abnormalities (Lavernia et al., 2015). Type 2 diabetes treated early with two glucose-lowering medications could postpone the need for insulin and halt the deterioration of blood glucose levels. This medication was just as effective as metformin by itself and was just as well-tolerated as a single treatment. We do not yet know the long-term effects of this early combo treatment (Matthews et al., 2020). Four classes of oral antidiabetic medications, including older and newer medicines, and influencing factors were examined in patients transferring from metformin monotherapy to metformin-based combination therapy (Kim et al., 2019). The conventional method of treating Type 2 Diabetes (T2DM) entails changing one's lifestyle and taking one oral glucose-lowering medication. Unfortunately, this strategy has drawbacks like a lack of glycemic stability and the possibility for harmful consequences at large dosages. Conversely, oral combination therapy can be administered as a mix of different drugs or as single-pill formulations (FDCs). Compared to multiple-pill combinations, single-pill FDCs have advantages in terms of cost, efficacy, and simplicity. But just as it might not be appropriate for

every patient, the gradual method might not be appropriate for every patient. Two frequently used combinations for the treatment of type 2 diabetic mellitus (T2DM) are metformin and sulfonylurea. In the US, 22.1% of metformin users also took a sulfonylurea in 2012. However, the risk of hypoglycemia, weight gain, and cardiovascular death may prevent some people from using both medications together. Another alternative is TZDs, however there is a chance of bone fractures and congestive heart failure with these. Although pioglitazone, an insulin sensitizer, has been demonstrated to enhance β-cell activity in individuals with type 2 diabetes, its use has not increased. In addition, DPP-4 inhibitors have been investigated in conjunction with metformin to enhance glycemic management and lower blood pressure and body weight. They do, however, come with a higher risk of genital mycotic infections, especially in women. Though these inhibitors are not licensed for the treatment of type 1 diabetes (T1DM), the US FDA warned people undergoing SGLT2 inhibitor therapy in 2015 to be aware of potential indications of diabetic ketoacidosis (DKA) (Lavernia et al., 2015b).

7.1 Metformin and Sulfonylureas

Sulfonylurea (SU) and metformin together are a commonly used combination that can lower HbA1c by 0.8–1.5%. It is linked to lower mortality from cardiovascular diseases and all causes combined. Due to unmeasured confounding variables, the rate of cardiovascular disease events is higher among SU users than in metformin users (Rojas & Gomes, 2013b). When used with metformin, sulfonylureas raise the risk of significant hypoglycemia episodes and all-cause mortality, indicating that newer oral hypoglycemic agents (OHAs) would be preferable for glycemic management (Hougen et al., 2021).

7.2 Metformin plus Insulin

Adding metformin to insulin-based regimens improves glycemic control, reduces the occurrence of hypoglycemia, and reduces the need for insulin, allowing for a 15–25% reduction in the overall amount of insulin administered (Rojas & Gomes, 2013c). Without having a substantial negative impact, metformin and insulin combination therapy improves glycemic control, reduces insulin requirements, and may enhance risk profile in people with type 2 diabetes (Ponssen et al., 2000).

7.3 Metformin and Thiazolidines

Type 2 diabetes mellitus (DM2) is characterized by increased hepatic gluconeogenesis, aberrant pancreatic beta cell function, and insulin resistance. Normal glucose tolerance progresses to impaired glucose tolerance (IGT), which leads to hypertension, dyslipidemia, and endothelial dysfunction. Cardiovascular disease is the primary source of morbidity in persons with DM2. Biguanides and thiazolidinediones are examples of oral medications that reduce insulin resistance and may be beneficial to the heart. When used with TZDs, metformin addresses important DM flaws (Stafford & Elasy, 2007). The care of chronic illnesses, especially diabetes mellitus—a disease marked by persistent hyperglycemia brought on by insulin resistance or deficiency—has been greatly enhanced by combination therapy. Worldwide, the prevalence of type 2 diabetes with insulin resistance is rising (Goyal et al., 2023). Tiered care progression is frequently used for initial treatment, with medical therapy, diet, and exercise serving as the foundation before moving on to oral glucose lowering medications. which combines metformin and thiazolidinediones—is for treating type 2 diabetes since it greatly enhances glucose regulation without inducing hypoglycemia or boosting insulin production. Nonetheless, there is ongoing discussion on the usage of thiazolidinediones both domestically and internationally (Saleh et al., 2009). Patients with

substantial insulin resistance are treated for type 2 diabetes with metformin and thiazolidinediones. While TZDs boost insulin-stimulated glucose disposal into skeletal muscle, metformin decreases the release of glucose from the liver (Brunmair et al., 2004).

Table 1: Combination of diabetic drugs in bilayer tablets (C Rubina Reichal & M Gopal Rao, 2017)

Combination of Drugs	**Brand Name**	**Reason**
Glibenclamide +Metformin HCL	Glucovance	• Reduce the frequency of administration • Improve the patient compliance
Pioglitazone+ Metformin HCL	Actoplus Met	• Improve the patient compliance
Metformin HCL +Gliclazide	GLUMETZA(R)	• Prolong the release up to 12hrs and improve the patient compliance
Glimepiride + Metformin HCL	Amaryl M	• Improve oral therapeutic efficacy with optimal control of plasma drug level
Glipizide +Metformin HCL	METAGLIP	• Provide synergistic action

7.4 Metformin and Pregnancy

For pregnant women with polycystic ovarian syndrome, gestational diabetes mellitus, and even non-diabetic obese women, metformin is a safe and efficient therapy choice (Verma & Mehendale, 2022). Worldwide prenatal metformin use is rising as a result of randomized controlled trials (RCTs) demonstrating the medication's efficacy and safety. Less maternal weight gain, good patient acceptability, and pregnancy outcomes comparable to insulin therapy were observed in the Metformin in Gestational Diabetes (MiG) randomized controlled trial. Metformin is also prescribed to obese non-diabetic women and those with polycystic ovarian syndrome. There have been no reported miscarriages or congenital abnormalities (Hyer et al., 2018). Pregnant women who take metformin had better results than those who follow a restricted diet, yet there is ongoing discussion over its superiority over insulin. Metformin use in gestational diabetes mellitus (GDM) is not substantially linked to poor mother or newborn outcomes, its use has expanded recently, despite the fact that several international clinical recommendations do not endorse it. Insulin is recommended by medical groups as the first-line treatment for GDM, in addition to lifestyle modifications (Jorquera et al., 2020).

7.5 Metformin use in Childhood and Adolescence

Childhood and teenage obesity and overweight are major public health concerns, with teens frequently developing into obese adult research (Olokoba et al., 2012). Obesity in children raises the chance of developing long-term conditions including diabetes, hypertension, heart disease, and cancer. In 2013, 23–38% of boys and girls in wealthy nations and 12–9% of those in developing countries were overweight or obese, indicating a considerable increase in prevalence (Sadeghi et al., 2020). The rising rate of childhood obesity forces clinicians to handle comorbidities. The American Diabetes Association advises treating children with prediabetes, screening children at high risk, and putting lifestyle modifications into practice.

The only oral medicine licensed for the treatment of diabetes in children, metformin, has positive benefits on body weight (Khokhar et al., 2017). It is anticipated that 5% to 10% of people with prediabetes advance to overt diabetes each year, including micro- and macrovascular problems. By using lifestyle changes and medicines to slow the shift, early detection of prediabetes can help focus resources and interventions on individuals most at risk of developing diabetes (Khokhar et al., 2017b). In children and adolescents, metformin may lessen the metabolic, endocrine, and cardiovascular abnormalities brought on by obesity. But over time, its efficacy wanes, and individuals with higher BMIs and insulin resistance benefit more from it. The impact of metformin in obesity and cardio-metabolic risk needs to be established through larger, longer-term controlled research (Soliman et al., 2020).

Chapter 8

Additional Benefits of Metformin

Due to its ability to lower blood sugar levels, metformin has many advantages, including the treatment of type 2 diabetes, weight loss, and cancer prevention. It can also lower blood pressure, cholesterol, and the risk of heart disease (Shortsleeve, 2024). By lowering insulin levels and encouraging the release of eggs from the ovary, metformin can increase fertility. Although it can be paired with clomiphene, it works best when used alone to help people become and stay pregnant. Additionally, metformin may enhance male infertility therapies and increase male fertility in obese individuals. Metformin increases immunity and lengthens life in rodents; nevertheless, it may lower the chance of dying young in people from specific illnesses (DeFronzo et al., 2015). Even in those without diabetes, metformin has been demonstrated to help treat obesity and metabolic syndrome by lowering body weight and waist circumference. The largest study to demonstrate the benefits of metformin on weight is the Diabetes Prevention Study. It's not yet known if it can stop cancer in real individuals, but it has also been shown to decrease tumor growth in lab models. Metformin has been demonstrated to lower the risk of colon cancer in diabetics, enhance the treatment of prostate cancer, and lower the incidence of breast cancer in those with Type 2 diabetes (Lin & Sun, 2010). Metformin has been associated with lower COVID-19 death rates in obese and female patients. Additionally, it can reduce the risk of diabetes by 18% after 15 years and by 30% in people with metabolic syndrome. However, metformin is not advised for those with COVID-19 diagnoses because there is no proof that it prevents dementia. As such, it ought to be regarded as a component of a health care plan (Ginns, 2018).

8.1 Current use of Metformin

When combined with a healthy diet and moderate exercise, metformin can help treat high blood sugar in patients with type 2 diabetes. It can also prevent kidney damage, blindness, nerve difficulties, problems with sexual function, and lessen the risk of heart attacks and strokes (WebMD, 2019). The prevalence of diabetes is rising worldwide, and the number of undiagnosed cases is rising as well. Comprehending the many pharmacotherapies that are available and minimizing their impact on the cardiovascular system are essential for managing diabetes. Diabetes patients who are admitted to hospitals frequently experience serious cardiovascular and in-hospital problems, which raises the overall fatality rate. Since diabetes exacerbates atherosclerosis and raises the risk of cardiovascular disease (CVD), metformin is not the first-line treatment for diabetes (Good & Pogach, 2018). Diabetic patients may initially present with peripheral artery disease, heart failure, angina, or nonfatal myocardial infarction as a result of cardiovascular disease. T2DM patients are more likely to experience renal impairment; of those with T2DM, 50% have some indications of chronic kidney disease (CKD) even in the absence of a history of proteinuria or diabetes. Nowadays, medical societies emphasize the unique traits and co-occurring conditions of each patient to lower the risk of CVD or CKD. Metformin is a desirable alternative because more recent antidiabetic medications, such as SGLT-2is and GLP-1RAs, have demonstrated encouraging effects in enhancing glycemic control, decreasing hypoglycemia and weight gain, and maybe delaying the advancement of CVD and CKD (C. González-López & Wojeck, 2023).

8.2 Metformin and Cancer

Metformin is known to potently suppress the proliferation, survival, and metastasis of various tumor cell types, such as those from lung, breast, liver, pancreatic, endometrial, colorectal, and kidney malignancies. Both AMPK-dependent and -independent pathways, including as AMPK

activation, mTOR signaling inhibition, and mitochondrial complex I suppression, mediate its anti-cancer actions. Metformin regulates angiogenesis, fibroblasts, tumor-associated macrophages, and immunosuppression, which changes the tumor microenvironment (Yanuar, 2017). It also acts as an anti-diabetic drug by inducing an immunological response, decreasing NF-κB activity, and lowering plasma glucose levels. DICER expression is also induced, which is important for microRNA biogenesis. The combination of metformin and hypoglycemia brought on by fasting reduces the metabolic plasticity and growth of tumors, indicating that tumor cells can adjust to changes in their metabolism. One new method of limiting diet through intermittent fasting aims to prevent tumor growth. (Lv & Guo,2020). Metformin functions by increasing insulin sensitivity in cells, controlling blood sugar, lowering hepatic glucose release, and delaying intestinal glucose absorption. It does not raise the production of insulin, which is advantageous because insulin is linked to an increased risk of obesity and cancer, which lowers the requirement for insulin (Ginns, 2018b). The primary mechanism of metformin's anticancer activity is its suppression of the mTORC1 pathway, which is essential for the metabolism, growth, and proliferation of cancer cells (Kasznicki et al., 2014).

Chapter 9

Adverse effects

Metformin therapy frequently results in adverse symptoms linked to the digestive system, such as loss of appetite, vomiting, diarrhea, and stomach pain, all of which usually go away when the medication is stopped or reduced (Shurrab & Arafa, 2020). Common adverse effects of the medicine metformin include constipation, diarrhea, stomach pain, and decreased appetite. For people with kidney problems, it is not advised, and the outer layer of an extended-release tablet may pass through the stool. Infections of the urinary tract are also possible. Metformin use over the long term has been linked to a higher chance of Alzheimer's and Parkinson's disease (Davis, n.d.).

9.1 GI effects

Common adverse effects of the medicine metformin include nausea, diarrhea, and pain in the abdomen. If these adverse effects are taken with food and tapered down gradually, they may be less severe (F et al., n.d.). The medication can be started a reasonable 500 mg twice day dosage and raised every one to two weeks until the highest dose that is tolerated is obtained. However, significant gastrointestinal distress accounts for about 5% of treatment discontinuations (Baker et al., 2021).

9.2 Lactic Acidosis

The drug metformin carries a boxed warning on its label regarding lactic acidosis, a significant side effect. This is a medical emergency requiring rapid hospital treatment due to a pH imbalance brought on by a buildup of metformin. Severe exhaustion, weakness, loss of appetite, nausea, vomiting, dyspnea, vertigo, and muscle aches are some of the symptoms (Kaneto et al., 2021). Up to 50% of people with metformin-associated lactic acidosis are

thought to die from it. The risk may be increased by other metformin-containing drugs (Perez, 2024). Patients with significant medical conditions, recent surgical procedures, low oxygen levels, heavy alcohol use, dehydration, and People over 80 are more likely to develop lactic acidosis, a common illness that arises from drug overdose or certain contraindicated circumstances (Nasri & Rafieian-Kopaei, 2014).

9.3 B12 Deficiency

Patients who have been using metformin consistently for a long period have been documented to have pernicious anemia due to a vitamin B12 deficiency. A patient with type 2 diabetes and a vitamin B12 level of 97 pmol/l was thought to have subacute combination cognitive impairment and spinal cord degeneration. Replacing the vitamin B12 restored normalcy to the hemoglobin anomalies and diarrhea (Foretz et al., 2023). Physicians should be aware that patients with diabetes, cognitive impairment, or blood diseases may have vitamin B12 insufficiency as a result of metformin. (Shurrab & Arafa, 2020b). Anemia and peripheral neuropathy can result from a B12 deficiency, especially when taking metformin. Maintaining B12 levels can be facilitated by routine check-ups and the use of foods high in B12, such as dairy products, beef liver, clams, poultry, eggs, and fortified cereals. Supplements can also aid in returning levels to normal, but you should speak with a doctor about them first (Davis, n.d.-b).

9.4 Metformin Contraindications

Among the contraindications are acute or chronic metabolic acidosis, congestive heart failure, metformin hypersensitivity, renal impairment, and impaired hepatic function (Tahrani et al., 2007). Although metformin is used to treat type 2 diabetes, it should not be taken if a patient has advanced age, congestive heart failure, or renal impairment. Because of the possibility of lactic acidosis, a rare metabolic acidosis, renal impairment is contraindicated. Recent research,

however, indicates that metformin may be taken safely up to fewer than 30 milliliters per minute of glomerular filtration; in this case, a dosage reduction to 45 ml/min is recommended (Mahmood, 2021). people who have concomitant cardiac failure and type 2 diabetes are usually not given congestive heart failure; nevertheless, new research indicates that these people may benefit from treatment (Mestrovik, 2011).

Chapter 10

Conclusion

Metformin is the first-line treatment for persons with type 2 diabetes since it has been found to reduce macrovascular outcomes when paired with lifestyle modifications in pre-diabetes and insulin-resistant phases of the disease. Although lactic acidosis raises problems, there is evidence to support its usage, and it is becoming more and more popular as a possible treatment for neurodegenerative illnesses like Alzheimer's. A dimethyl biguanide drug called metformin is used as a first-line antihyperglycemic medication to treat Type 2 Diabetes (T2D). It doesn't cause genetic, mutagenic, or reproductive harm when taken in accordance with the recommended dosage. To improve oral bioavailability and minimize possible adverse effects, novel formulations have been required due to its pharmacokinetic characteristic. The pharmacological action of metformin in reducing hyperglycemia is directly linked to its capacity to inhibit intestinal and hepatic glucose absorption, improve peripheral insulin sensitivity, and stimulate β-cell activities. Finding novel anti-diabetic medications may be facilitated by gluconeogenesis targeting. The multi-targeting of metformin has been demonstrated, which adds to its clinical benefits of cardio protection, long-term safety, and efficacy. When treating different types of diabetes and metabolic illnesses, metformin is safe, effective, and cardioprotective; nevertheless, dose and individual response must be carefully considered. Novel molecular processes and cancer action are examples of current advancement.

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