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A Comparison between Metformin Immediate-release and Extended-release: A Review

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ABSTRACT— Metformin is the first-line oral therapy for type II diabetes; it comes in various forms that can be used alone or with other oral hypoglycemic medications. The National Institute for Health and Care Excellence guidelines recommended starting with Metformin immediate-release and shifting to extended-release when not tolerated. We aimed to compare the immediate and extended-release formulation in terms of metabolic profile, gastrointestinal adverse effects, patients' satisfaction, and health-related quality of life. The extended-release formulations were better in terms of gastrointestinal side effects. In addition, it improved patients' satisfaction and adherence to treatment. There were no significant differences between Metformin-immediate release (MIR) and Metformin-extended release (MXR) regarding body mass index and waist circumference. The effect on lipid profile was modest; a reduction of low-density lipoproteins, total cholesterol, and an increasing high-density lipoprotein were observed with no statistical significance between the two formulations. However, a rising triglycerides was found among patients taking the extended-release. The evidence is conflicting regarding glycemic control. Six out of the eight included studies showed similar efficacy, one showed the superiority of the immediate-release, and another one showed that the extended-release was more effective. Therefore, studies into hypoglycemia risk and lactic acidosis are definitely needed to address all these conflicting situations.

KEYWORDS: Metformin, immediate-release, extended-release, metabolic effects, quality of life.

1. INTRODUCTION

Diabetes mellitus (DM) is rising worldwide; it already affects 9.3% of the adult population. The projections for 2030 and 2045 are 10.2% (578 million) and 10.9 percent (700 million), respectively [62]. According to the International Diabetes Federation, the Kingdom of Saudi Arabia has one of the highest diabetes prevalence rates (18.7% of the population has diabetes) [119].

Metformin is the first-line oral therapy for type II diabetes; it comes in various forms that can be used alone or with other oral hypoglycemic medications. Metformin immediate-release is commonly taken with meals numerous times, with the action peaking three hours after the 1000mg dose [3]. Metformin extended-release was introduced to address the frequent dosage of Metformin immediate-release and was found to enhance compliance [81].

Metformin formulations generally have comparable pharmacokinetic characteristics. However, Metformin extended-release peaks (two grams) seven to eight hours after the dose. Despite the lack of direct

comparisons between Metformin immediate-release and Metformin extended-release, a few earlier studies indicated Metformin extended-release to have better adherence and fewer gastrointestinal side effects [3], [38].

Many Metformin users experience gastrointestinal side effects. In a trial of elderly patients, there was no difference in adverse reactions between different Metformin doses (1000 mg and 2000 mg); however, greater doses improved glycemic control [141]. Patients with a particular phenotype, such as ABO group imbalance, left-handedness, and an iron load, had severe Metformin intolerance that led to drug discontinuation [48].

Glycated hemoglobin of 7% is proposed by the American Diabetes Association and the European Association for the Study of Diabetes [83], [140]. Tighter glycemic control was preferred in young, newly diagnosed patients, but elderly patients with comorbidities required a more flexible approach. To avoid diabetic complications such as retinopathy, neuropathy, and nephropathy, strict control of blood glucose and glycated hemoglobin in the normal or near-normal range was essential [37].

Diabetic dyslipidemia is characterized by an increase in triglycerides (TGs), a decrease in high-density lipoprotein cholesterol (HDL-C), and a decrease in small-dense (atherogenic) low-density lipoprotein cholesterol (LDL-C) particles. The effects of Metformin on lipid profiles have been hotly debated, with some research reporting favorable results [84]. On the other hand, other research found no additional benefits [34].

Obesity is associated with diabetes mellitus. Metformin has been demonstrated to be weight neutral and may moderately lower the body mass index in older adults with diabetes [68].

Patients with diabetes should have their treatment satisfaction measured regularly. Metformin extended-release was linked to better adherence to therapy [122].

Metformin has been found to improve the quality of life in diabetics. However, direct comparisons of Metformin (IR) and (XR) are limited [17].

Few studies compared immediate and extended-release regarding metabolic indicators and patients' satisfaction. On the other hand, no studies have explored the quality of life, especially in the region of the study conduction. A direct interview, anthropometric measurements, and blood samples at baseline, three months, and six months are all potential challenges for the project. Extra costs may be required for expert data collectors, and the tests are not available at the local laboratory. The real-world nature of this study can assist both the treating physicians and policymakers in choosing the most appropriate Metformin formulation in terms of effectiveness and side effects.

2. LITERATURE REVIEW

Type II diabetes mellitus is the most common type of diabetes and constitutes 90 to 95% of diabetes. The disease leads to microvascular and macrovascular complications leading to substantial physical and psychological distress [117]. The International Diabetes Federation (IDF) first estimates of people living with diabetes were 151 million, which jumped to 463 in 2019. The expectation for the year 2045 is 963 million [7], [124]. Type II diabetes is essentially a vascular disease affecting both microvascular and macrovascular systems with substantial physical, psychological, and economic burdens on the patients and their families and healthcare providers [33].

The defect in type II diabetes is decreased secretion and sensitivity to insulin by various organs. Thus, the pathophysiology is not well understood. Although the pancreas (β-cells and α-cells) is the main site of insulin synthesis and regulation, the liver, skeletal muscles, brain, gut, and adipose tissue are blamed. In addition, the immune system, gut microbiota, and inflammation role is recently evolving [41], [111]. The gut microbiota diversity is thought of as a potential mechanism linking low-grade inflammation, intestinal barrier disruption, immune regulation, and the development of both diabetes mellitus and obesity. Therapies targeting gut microbiota, including fecal microbiota transplantation, may be helpful for therapeutic strategies for diabetes management [109], [139].

The increasing rate of obesity in the past decades is mirrored by an increasing rate of type II diabetes mellitus. Weight loss among patients with high body mass index leads to improvement in plasma glucose, and weight loss is a target for good diabetes control [106]. In mammals, white adipose tissue serves to store energy, while brown adipose tissue plays an essential role in maintaining body temperature. White adipocytes can differentiate into beige adipocytes with similarity to brown adipose tissue under stimulants like cold weather and exercise. Enhancing the differentiation of white adipocytes is a novel theory for decreasing insulin requirement and may be targeted as a diabetes treatment [19], [99]. Adipose tissue has been viewed as an endocrine system secreting not only leptin and adiponectin, but also more than twenty mediators of glucose, protein, and fatty acids. Adipose tissue plays a vital role in insulin resistance and type II diabetes [40].

Initial evidence showed that tight glycemic control reduces both microvascular and macrovascular complications and relies on glycated hemoglobin as a marker of glycemic control [104]. Recently, moderate-intensity glycemic control has been more important in reducing complications and improving quality of life [102], [103]. A patient-centered approach to diabetes care by shared decision, integration of patient´s needs, values, and preferences with evidence-based healthcare are basic. Metformin is the first-line oral hypoglycemic drug in the USA, while in Europe, the decision is based on cardiovascular risk factors [20].

2.1 Metformin Formulations

2.1.1 Metformin-Immediate Release (MIR)

Although Metformin has been widely used for a long time, the mechanism of action is to be elucidated. The drug was initially obtained from the plant Galega Officinalis, used in Europe as folk medicine, and approved in America in 1994 [47]. Metformin is absorbed by the plasma monoamine transporter and organic cation transporter 3 on the apical membrane, then metabolized in humans and secreted intact by the renal system. The drug is metabolized by the liver with a reduction in its concentration and delivered in the plasma [2], [75]. Metformin absorption is complete within six hours with a bioavailability ranging from 40-60%, and no protein binding, conjugation, or metabolites of Metformin were identified. The plasma elimination half-life ranged from 4.0 and 8.7 hours, and the dose ranged from 0.5 to 1.0 mg/L (fasting state) and 1 to 2 mg/L (after meals). Drug monitoring is of value only when lactic acidosis is suspected [44], [108].

Metformin treatment was found to reduce hyperglycemia among drug naïve patients with type II diabetes. The drug is weight neutral with minimal hypoglycemic effects [94]. A recent review and meta-analysis concluded that Metformin immediate-release (MIR) was more effective in reducing HbA1c than the extended-release formulation (MXR) at the expense of dyspepsia that was commoner among MIR [1]. [14] found similar efficacy of MIR and MXR regarding glycemic control. [45] conducted a randomized controlled trial. They used MIR 1000mg twice daily, MXR 1000mg twice daily, and MXR 500mg

twice/day and found a similar reduction in plasma glucose, while gastrointestinal side effects were higher among the MIR arm. Metformin act by inhibiting gluconeogenesis and increasing insulin sensitivity in peripheral tissues. The advantages of Metformin are its safety profile and cost-effectiveness [114].

The side effects of Metformin immediate-release are mainly gastrointestinal (namely, flatulence, dyspepsia, and diarrhea) and may affect patients' adherence to treatment and glycemic control [55]. Other side effects are vitamin B12 deficiency and the rare lactic acidosis. Lactic acidosis results due to the drug inhibition of the mitochondria, mainly in the liver, although lactic acidosis is rare. Thus, the drug is contraindicated in patients with renal impairment, advanced cirrhosis, and severe heart failure. Vitamin B12 deficiency is well established among Metformin users, but a routine prescription is not recommended [36], [71].

Studies on the effects of Metformin on lipid profile are many and showed conflicting results. [115], in their meta-analysis, showed a reduction of both cholesterol and low-density lipoproteins. Solymar and colleagues' results supported [22] meta-analysis, which showed the beneficial effects of Metformin on cholesterol, low-density lipoproteins, triglycerides, and high-density lipoproteins. The mechanism might be through the Carbohydrate-Responsive Element-Binding Protein and Proprotein Convertase Subtilisin/Kexin Type 9 [50]. Similar effects were reported by [138]. They investigated the effect of Metformin treatment on metabolite concentrations and concluded that Metformin activated AMPK and is associated with low-density lipoprotein reduction.

[66] assessed Metformin-induced oxidative stress and cholesterol biosynthesis and found an inhibitory effect on cholesterol biosynthesis similar to simvastatin. [129] reviewed the literature and reached exciting conclusions. The authors stated that Metformin's action might be mainly in the intestinal tract due to the higher concentration of the drug. In addition, the authors concluded that Metformin acts in parallel ways with statins and reduces LDL. In addition to its lipid-lowering effects, [95] reviewed the literature and demonstrated the anticancer and antiaging effects of Metformin. The mechanism is thought to be through the Metformin effect on adenosine monophosphate (AMP)-activated protein kinase. [80] confirmed Podhorecka and colleagues' findings and discussed the possible involvement of the immune modulation of Metformin mediated by Metformin on tumor progression. [90], [13] showed the beneficial effects of Metformin on colorectal cancer, while [133] concluded the possible beneficial effect on prostate cancer.

2.1.2 Metformin-Extended Release (MXR)

Metformin extended-release in its once-daily tablets is released at a controlled rate. Some controls showed that MXR reduces fasting insulin (a marker of insulin sensitivity) compared to the immediate-release [131]. The bioavailability of a single dose after an evening meal is similar to the immediate-release formulation in divided doses. However, the time to peak concentration in the plasma is longer [5]. In contrast to the immediate-release formulation, its bioavailability increases after food. The 500mg, 1000mg, 2000mg, and 2500mg once daily after the evening meal is similar to MIR in divided doses in terms of HbA1c reduction [98].

The optimal concentration-time curve of MXR reduced reactive hypoglycemia induced by MIR in a case reported by [4]. [26] conducted a randomized trial and showed that MXR was more in reducing glucose variability, insulin resistance, and some adipokines. The (XR) formulation is progressively absorbed and released in the upper gastrointestinal tract, enhancing tolerability and patient compliance. The drug is administered less frequently and might have fewer side effects [27].

National Institute for Health and Care Excellence (NICE) recommendation is to start with Metformin-

immediate-release and switch to extended-release if gastrointestinal develop [29]. The mechanism of Metformin action is complex and involves both the inhibition of mitochondrial respiration and lysosome (mitochondrial glycerophosphate dehydrogenase) [100]. Another mechanism of action of Metformin in the gut is the activation of glucagon-like peptides in the gut, which was observed in both immediate and extended-release [97]. An interesting phenomenon is the gut-liver-brain cross-talk mediated through the tractus solitarius and vagal efferent; the mechanism showed exposure to Metformin in the duodenum suppresses glucose production by the liver, thought to involve both glucagon-like peptide and AMP-activated protein kinase [24], [134].

Several studies found the lower gastrointestinal side effects. [42] conducted a randomized, open-labeled, positive-controlled multicenter study recruiting 150 Chinese patients and found increased adherence of Metformin extended-release, better glycemic control, and fewer gastrointestinal side effects. On the other hand, a recent randomized controlled trial and a multicenter study conducted in Canada and China showed similar safety profiles for the two formulations [57], [78].

[143] conducted an in-vivo and in-vitro study and found similar bioavailability of generic and branded formulations. The study findings were confirmed by a randomized, open, two-period trial conducted among thirty-four volunteers in China [120]. The above results imply that the generic and branded might be used alternatively. However, the studies were conducted in the same country. Further studies are needed to test the bioavailability of generic and branded formulations in different countries [55].

2.1.3 Metformin (XR) and The Gut Microbiota

Metformin extended-release with an outer hydrophilic polymer matrix system has the advantage of infrequent dosing and more adherence than the immediate-release. In addition to lesser gastrointestinal intolerance [16]. MXR is slowly absorbed in the gastrointestinal tract due to its long gastric residence; 90% of the drug is gradually released over ten hours in contrast to immediate-release (90% in thirty minutes) [63]. An interesting observation is that Metformin exerts accumulation of 18F-labeled fluorodeoxyglucose in the colon, and the substance remains in the gut for more than three days [73].

A double-blind, randomized, controlled clinical trial showed an increase in the abundance of Akkermansia Muciniphil and Bifidobacterium Adolescentis species that correlates with improved glycemic control [135]. Metformin tolerance or intolerance of patients with diabetes may be influenced by their microbiota diversity [128]. The above findings imply that Metformin action is mediated at least partially through the gut microbiota [118]. Metformin effects on gut microbiota indicated that microbiota might be a promising target for treating diabetes mellitus type II and its associated dyslipidemia [125].

National Institute for Health and Care Excellence recommended that patients with diabetes start with Metformin immediate-release and switch to extended-release [29]. Many patients with type II diabetes cannot tolerate Metformin in the desired doses due to unwanted gastrointestinal side effects, even when started with minimal doses [16]. Gastrointestinal (GI) side effects of Metformin were described as mild or moderate and occur in one in five of the patients (bloating, nausea, diarrhea, and vomiting) [10]. In addition, 5% of patients are not able to tolerate Metformin at all; the side effects cannot be predicted due to the inter-individual variability [65].

The mechanism of gastrointestinal adverse events is unclear. [30] conducted a prospective cohort and showed organic cation transporter is involved in gastrointestinal adverse effects. The gastrointestinal adverse events are dose-dependent and can be reduced by initiating Metformin immediate-release in a small

dose and then escalating the dose gradually [54]. [141], [53] conducted randomized controlled trials among elderly patients with type II diabetes and patients with preexisting gastritis. They concluded that Metformin doses of 1000mg and 2000mg had the same gastrointestinal side effects. The authors suggest starting with 1000mg and titrating the dose to reach the desired HbA1c.

2.1.4 The Gut as A Primary Site of Action of Metformin

There is an increasing interest in glucose metabolism in the gut. Importantly, positron emission tomography showed an increasing fluorodeoxyglucose uptake in the gut, especially the colon [86]. Interestingly the uptake was not observed in the first two days of Metformin administration. However, this persisted after 30 days of Metformin intake and continued after withdrawal of the drug [24]. Metformin is associated with gastrointestinal side effects in nearly one-third of the patients, and a considerable percentage develop severe adverse effects necessitating discontinuation of the drug [65]. The high concentration of Metformin in the intestine might explain the side effect because y slow-release formulations of Metformin have lower GIT side effects [31]. Other mechanisms may involve reducing serotonin transport via the serotonin transporter or stimulating serotonin release from enterochromaffin cells, and increasing serotonin luminal concentration [32].

2.1.5 A Comparison between Metformin (IR) and (XR) Side Effects

The gastrointestinal side effects of Metformin immediate and extended-release were discussed controversially. [29] from the United Kingdom conducted a retrospective cohort and found fewer gastrointestinal side effects in the Metformin extended-release arm. [42] found similar results among 150 Chinese patients who were randomized to Metformin extended-release and Metformin immediate-release. On the other hand, the results from the CONSENT trial that was conducted among drug-naïve Chinese patients showed a similar safety profile. The better tolerability of Metformin extended-release might be explained by the delayed entry into the systemic circulation [57].

2.1.6 Glycemic Control

The liver is the principal organ of glucose metabolism and storage. About 200mg is stored in this vital organ, released in the fasting state, and reflected in fasting plasma glucose [46]. After meal ingestion, the carbohydrates are absorbed and reach the circulation reflected by the postprandial blood glucose. The pancreas is the source of insulin secretion to regulate the glucose metabolism in both the fasting and after-meal [82]. The plasma glucose is regulated by the pancreas, the liver, the intestinal tract, and the renal system [136].

The vital determinant of glycemic control is glycated hemoglobin (HbA1c). HbA1c reflects the patient's average blood glucose over two to three months and strongly predicts mortality and microvascular complications [69]. After demonstrating the relationship between glycemic control and glycated hemoglobin, many tests are used to assess its concentration [132]. However, the test needs standardization to the NGSP and is not without limitations. The test is affected by the red blood cells turnover and is not accurate in patients with hemoglobinopathy, including sickle cell anemia and thalassemia. In addition, patients with renal impairment and hemolysis are not candidates for the test [23], [77].

Glycemic control provides good reflection to the patients and healthcare providers; it is a basic indicator of diabetes microvascular complications. The European Association for the Study of Diabetes and the American Diabetes Association recommend HbA1c measurement every six months and three months in patients with good and poor glycemic control, respectively [87], [113]. Glycemic control can be monitored by random plasma glucose in critically ill patients, and maintaining a level of ≤ 180mg/dl was shown to

reduce mortality with minimal hypoglycemia risk [49]. Both plasma glucose variability and the glycated hemoglobin (HbA1c) variability were shown to increase microvascular and macrovascular complications and mortality rates. Thus, glycemic variability plays a role in clinical risk assessment [43].

Blood glucose levels vary according to fasting and meal taking, while HbA1c evaluates the average glycemic control over three months (the average lifespan of the red blood cells). In addition, the test requires no fasting and is more familiar to most patients [9]. Prior trials with a long follow-up period (Diabetes Control and Complications Trial and UK Prospective Diabetes Study) observed the association of HbA1c and diabetic retinopathy, nephropathy, and neuropathy [21], [116]. However, a study conducted among Korean adults and youth groups showed a discrepancy between HbA1c and fasting blood glucose [64].

Despite the substantial advances in diabetes therapy and the introduction of new antidiabetic medications, a substantial percentage of patients with diabetes are not reaching the recommended glycemic target. The American diabetes association recommended glycated hemoglobin of <7 in most patients with a more tight or flexible approach depending on comorbidities, age, and risk of hypoglycemia [8], [11]. The HbA1c target is better individualized based on the patient's characteristics and preferences, the risk of adverse events, the presence of comorbidities, and life expectancy (usually from<6.5 to 8) [88].

Poor glycemic control is the leading cause of microvascular complications. A study conducted in the USA showed that 7.3 billion more costs due to therapeutic inertia (1-year time horizon) and loss of approximately 13,390 life-years [6]. Similar findings of increasing economic burden were observed in Denmark, and delaying the treatment intensification leads to loss ranging from 72 to 384 Danish kroner (DKK) [76].

2.1.7 A Comparison between Metformin (IR) and (XR) Effects on Glycemic Control

Glycemic control has been discussed by a great number of authors in the literature. A randomized control trial conducted in Pakistan showed similar efficacy of Metformin immediate-release and extended-release [45]. An international, randomized, double-blind trial with a duration of 24 weeks and published by [3] confirmed the above observations. [57] recruited 532 patients and randomized them to either MXR or MIR for four weeks with two weeks of follow-up off treatment and showed no difference between the two arms. On the other hand, a randomized control trial with a six-month follow-up period showed the superiority of the extended-release preparation over the immediate-release. Notably, the trial was conducted among Caucasians [26].

[1] conducted a meta-analysis including 2609 patients in nine randomized controlled trials and found that Metformin immediate-release was better in HbA1c lowering. Another meta-analysis included five randomized trials and showed the similar effectiveness of Metformin (XR) and (IR) formulations regarding glycemic control [122]. Another meta-analysis included fifteen studies with no restriction to the language and showed similar effects of MIR and MXR on fasting plasma glucose and glycated hemoglobin. However, the quality of the included studies limited their findings [123].

A study conducted in 2003 among patients already on Metformin immediate-release who were then shifted to extended-release in different doses (the same or higher) showed a similar reduction in the glycated hemoglobin at six months [39]. An interesting study investigated the effects of patients on MIR and other hypoglycemic drugs and were switched to MXR at a smaller dose. The glycemic control worsens and returns to its original value when escalating the dose to that equivalent to MIR [14]. The evidence from meta-analysis is conflicting regarding the effects of MIR and MXR on glycemic control [63]. A plausible

explanation might be the differences in the study duration and the country of origin (ethnicity). The character of the patients (drug naïve or already on the oral hypoglycemic drug) might also affect the results [3], [72].

2.1.8 Lipid Profile

Lipid abnormalities are the major cardiovascular risk factor, and diabetes mellitus is characterized by an increasing amount of dense low-density lipoproteins, low high-density lipoproteins, and high triglycerides. Glycemic control has only a modest effect on low-density lipoproteins while elevating the level of triglycerides and decreasing high-density lipoproteins [15], [130]. Diabetes mellitus exerts both qualitative and structural changes in low-density lipoproteins. The prolonged retention of LDL in the plasma increases their uptake by the macrophages, thus forming foam cells and atherosclerosis. Triglyceride /low-density-lipoprotein cholesterol ratio might be more reliable than non-HDL-C in type II diabetes patients not treated with statins [15], [101].

The effects of the immediate and extended-release Metformin on lipid profile are essential due to the increasing atherosclerotic heart disease among patients with type II diabetes [96]. [25] conducted two randomized double-blinded controlled (parallel-group) trials in the United States of America and found a reduction in total cholesterol and low-density lipoproteins. [137] conducted a systematic review and meta-analysis; the analysis included forty-one studies and found that Metformin decreased significantly in plasma triglycerides, total cholesterol, and LDL cholesterol.

2.1.9 The Metformin Paradox

[39] shifted the patients from immediate-release to extended-release formulation of Metformin and found a significant increase in triglycerides. [38] conducted another placebo-controlled trial of six months duration and showed increasing levels of triglycerides with lowering effects on total cholesterol and low-density lipoproteins. The combination of Metformin and statins was shown to be synergistic and ameliorated diabetic cardiomyopathy by inflammation, apoptosis, and oxidative stress inhibition [58]. Both Metformin and statin may negatively affect skeletal muscle response to exercise; recent studies showed that combining both drugs might help in blunting progressive resistance training-induced by Metformin. Therefore, the combination is helpful in sarcopenia (a significant problem with aging) prevention [52], [79].

2.1.10 A Comparison between Metformin (IR) and (XR) Effects on Lipid Profile

[42] conducted a study among 150 Chinese patients who were randomized to Metformin extended-release (MXR) and Metformin immediate-release (MIR) and found comparable effects on lipid profile. [3] conducted a face-to-face comparison of Metformin (XR) and (IR) and found no difference in body mass index, lipid profile, and waist circumference. [110] showed minor changes in cholesterol, low-density, and high-density lipoproteins. In addition, the authors reported an increased level of triglycerides among extended-release formulations. [74] shifted the patients from immediate to extended-release; they found that the extended-release achieved the same metabolic targets with smaller doses and lower GIT side effects.

2.2 Body Measurements

2.2.1 Body Mass Index

Body mass index was used for more than thirty years for the classification of obesity and overweight. Body mass index is reliable in body weight excess but cannot differentiate between lean mass and fat [92]. A simple parameter of abdominal adiposity in the waist circumference is a better indicator of visceral adiposity and obesity-associated diabetes risk [89]. Visceral adiposity tissue and visceral adiposity index (combining body mass index and waist circumference with triglycerides and high-density lipoproteins) are

better surrogates of insulin resistance [91].

Metformin was shown to reduce body weight in obese patients without diabetes; the weight reduction was more among patients with insulin resistance independent of baseline body mass index, age, and sex [112]. A meta-analysis of randomized control studies showed that Metformin was effective in reducing body mass index among patients with metabolic liver disease [51]. However, the changes were similar to the control arm. [85] conducted a meta-analysis of twenty-four randomized controlled trials and concluded the uncertainty regarding the effects of Metformin on obesity.

2.2.2 Waist Circumference

The waist circumference is measured in a standing position, and removing heavy clothes is a good predictor of insulin resistance than body mass index [105]. [74], who shifted the patients with type II diabetes on Metformin immediate-release (alone or in combination with other oral hypoglycemic drugs), found no effect on waist circumference after six months of follow-up. Similarly, [39] found no differences between Metformin immediate and extended-release in waist circumference, glycemic control, and other metabolic parameters.

2.2.3 A Comparison between Metformin (IR) and (XR) Effects on Body Mass Index

A recent review and meta-analysis included fifteen studies (3765 respondents). They found a non-significant statistical difference in body mass index among patients who were randomized to Metformin (IR) and (XR) [123]. The previous observations supported the findings of [42]. They randomized 150 subjects into the MXR and MIR groups and found comparable efficacy of the two formulations regarding body mass index. A similar reduction in body mass index was observed by [26], who enrolled 253 patients with uncontrolled diabetes mellitus after six months of follow-up.

2.2.4 Treatment Satisfaction

Treatment satisfaction among patients with type II diabetes is vital for drug adherence and better glycemic control to avoid microvascular complications [56]. Most patients developed gastrointestinal adverse effects while using Metformin; gastrointestinal side effects are the major causes of non-compliance and treatment discontinuation [63]. Extended-release formulation with one/day administration was developed to overcome the gastrointestinal side effects and improve patients' compliance [55].

A significant problem of Metformin (XR) is the insoluble external shell of the pill (known as the Ghost pill). The Ghost pill is non-absorbable and excreted unchanged in the feces, causing anxiety and mistrust among the patients and their healthcare providers. Although the Ghost pill does not affect its absorption or efficacy, a sensitive manner is needed to handle this issue [67], [127]. Other major concerns are the tablets' size, shape, taste, and burst of absorption observed with Metformin extended-release; a prolonged release was developed to overcome these unwanted effects and improve compliance [60].

2.2.5 Policies to Overcome Non-Adherence

Many interventions were developed to improve Metformin's non-compliance and patients' satisfaction. [18]. [27] found that the powder formulation improved the Diabetes Quality of Life questionnaire, increased the patients' satisfaction, and improved metabolic profile. Another formulation is the prolonged-release Metformin, which improves patients' adherence and satisfaction in real-world studies. Mesoporous silica nanoparticles Metformin mixture is another formula to form a quasi-spherical pellet and prolong the release [93].

2.2.6 A Comparison between Metformin (IR) and (XR) Effects on Treatment Satisfaction

Evidence from the meta-analysis showed that Metformin extended-release improved patients' satisfaction and adherence to treatment [122]. The infrequent and low dosing were the reasons behind adherence. [29] conducted an observational study in the United Kingdom and stated that the adherence increased from 62% to 81% when the patients were shifted from immediate-release to MXR formulations. [55] published a study in the USA; and concluded that Metformin extended-release had the potential to improve the patients' satisfaction and adherence due to its simple dosing regimen.

2.2.7 Quality of Life

Quality of life refers to a person's perception of physical, emotional, and social status. The reduced quality of life among patients with type II diabetes due to complications has recently gained prominence. Many measures were introduced to measure diabetes quality of life, including the Summary of Diabetes Self-Care Activities Scale (SDSCA) and the Diabetes Treatment Satisfaction Questionnaire [28], [126]. Metformin was shown to improve the quality of life among patients with diabetes. However, face-to-face comparisons between Metformin IR and XR are lacking [17].

Patients with type II diabetes reported poor physical and mental health, and their quality of life is lower due to a lack of support, resilience, post-traumatic stress, and coping [107]. A systematic review and meta-analysis of 18 studies showed that depression, hypertension, initiating lifestyles, and diabetes complications were the major determinants of poor quality of life among patients with type II diabetes [61]. Patients with comorbidities had a lower quality of life than patients without. [59] showed that people with type II diabetes alone experienced better quality of life than those with diabetes and hypertension.

Studies of Metformin's effects on quality of life are scarce; a study published among elderly patients with type II diabetes showed that Metformin and physical activity improved quality of life but not Metformin alone [12]. [35] conducted a study among 360 patients with newly diagnosed type II diabetes. They found that abdominal pain, bloating, and nausea are the major determinants of low physical and mental health-related quality of life. A further case-control study showed a negative impact of Metformin-induced gastrointestinal adverse effects on the physical component of health-related quality of life [142].

2.2.8 A Comparison between Metformin (IR) and (XR) Effects on Quality of Life

Literature comparing Metformin immediate and extended-release lacks. [74] shifted the patient from Metformin immediate-release to the extended-release formulation, and they stated that patients had a greater sense of well-being. [70] showed that Metformin improved health-related quality of life components (mainly the usual gait speed). The deterioration of quality of life is primarily due to gastrointestinal side effects. [121] conducted a case-control study among patients with diabetes mellitus. They found that patients with type II diabetes had poor quality of life mainly due to gastrointestinal adverse events.

3. CONCLUSION

The NICE guidelines are to start Metformin immediate-release and shift to extended-release if intolerance develops. The extended-release formulations were better in terms of gastrointestinal side effects. In addition, it improved patients' satisfaction and adherence to treatment. There were no significant differences between MIR and MXR regarding body mass index and waist circumference. The effect on lipid profile was modest; a reduction of LDL and total cholesterol and an increasing HDL were observed among the two formulations. However, increasing triglycerides were found in the extended-release. The evidence is conflicting regarding glycemic control, and studies on quality of life are scarce. Further randomized controlled trials with long-duration focusing on the effects of Metformin immediate-release and

extended-release on gut microbiota are recommended.

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